Chapter 6
Substitution Reactions of Alkyl Halides

After five chapters of preparation, we are ready to examine our first type of organic reaction. (In Chapter 4 we examined acid-base reactions, but these did not necessarily involve organic molecules.) Both this and the next chapter deal thoroughly with our first functional group: a halogen bonded to a carbon in an alkyl halide.

The subject of this chapter, nucleophilic substitution reactions of alkyl halides, does recall earlier work. While discussing nucleophiles and electrophiles in Chapter 4, we occasionally encountered examples of this type of reaction. With a mechanistic sense developed in Chapter 5, we can rationally apply the theory of nucleophiles and electrophiles to a very useful kind of reaction.

6.1 Notable Alkyl Halides

Alkyl halides are more common in nature than believed even ten years ago. Various plants produce chloromethane (CH_3Cl), chloroform ($CHCl_3$), bromoform ($CHBr_3$), and more complex alkyl halides, perhaps to discourage predators. In addition to their two important kinds of reactions, explored in Chapters 6 and 7, alkyl halides have many practical uses. A common dry-cleaning solvent is 1,1,1-trichloroethane (see Section 2.1D for the nomenclature of alkyl halides).
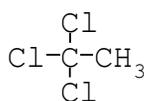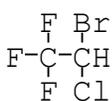
| 1,1,1-trichloroethane | Halothane | Freon-12 | DDT |
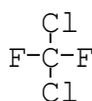
Dichloromethane (methylene chloride, CH_2Cl_2) is a common laboratory solvent and industrial degreaser. Halothane is an inhalation anesthetic, and chloroethane (CH_3CH_2Cl, bp 12°C) is a local anesthetic, which numbs by its fast, endothermic evaporation.   Freon-12 and other chlorofluorocarbons (CFC's) are refrigerants and aerosol propellants, which are no longer used because they lead to ozone depletion in the stratosphere (Section 23.5). Various chlorinated insecticides, such as DDT, have saved human lives by controlling insect infestations, while sometimes harming the environment. Evidence suggests that chlorinated compounds can mimic estrogens and diminish reproductive capacity in humans.
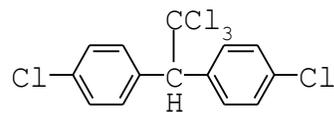
Some alkyl halides can be made by free-radical halogenation of alkanes (Section 23.2), but in the laboratory they are usually made from alkenes (Section 8.8A) and alcohols (Section 10.5C).

6.2 Physical Properties of Alkyl Halides

Let us next consider three of the physical properties of alkyl halides: boiling point, solubility, and density. Examine a plot of the boiling points for the smaller unbranched alkanes and their 1-haloalkane derivatives:
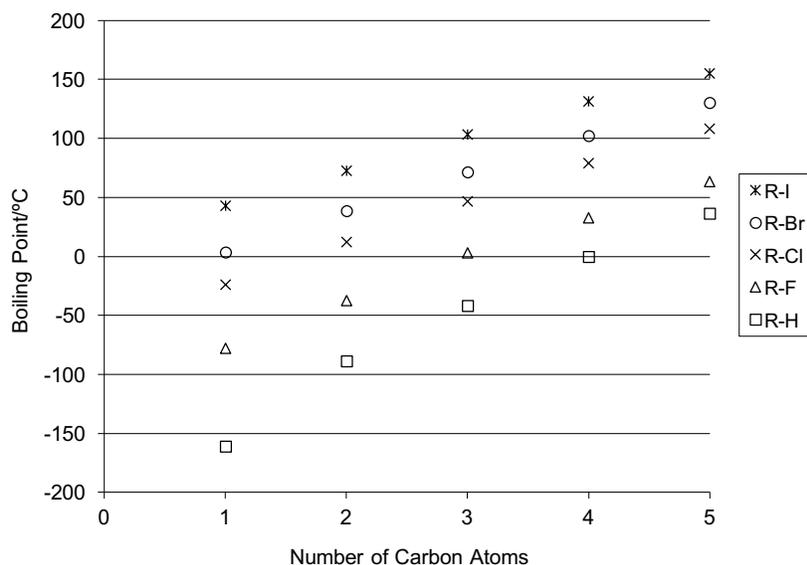
boiling points of unbranched alkanes and 1-haloalkanes

Note two important trends. Within one "family" of compounds (e.g., the alkanes, R-H, or the alkyl fluorides, R-F), as the number of carbons increases, the boiling point increases. Dispersion forces account for this phenomenon among alkanes (Section 2.5). These same forces operate among the alkyl halides. As the number of carbons increases, the surface area of the molecule and dispersion forces also increase. The increase in this intermolecular force raises the boiling point.

We can note a second trend in Figure 6.1. For a given number of carbon atoms, the boiling point increases from alkane to alkyl fluoride to alkyl chloride to alkyl bromide to alkyl iodide. Which intermolecular force increases during this change? The larger the halogen atom is, the greater the surface area of its molecule, and the greater the dispersion forces. Although dispersion forces often seem less important than dipole-dipole forces and hydrogen bonds, they can be a critical factor.

A second physical property of alkyl halides is their solubility in various solvents. What

kind of solvent should best dissolve these compounds? Consider the polarity of alkyl halides. A simple, monohalide has only one polar bond: the bond between the halogen and the carbon. Thus simple alkyl halide molecules have little polarity. Therefore, solvents of little or no polarity, such as diethyl ether or hexane, readily dissolve alkyl halides. In contrast, water is too polar to dissolve these compounds.

A third physical property of alkyl halides is density. Common unhalogenated solvents, such as diethyl ether and hexane, are less dense than water. In contrast, common halogenated solvents, such as dichloromethane and trichloromethane (chloroform), are denser than water because of their heavy halogen atoms. These two rules of thumb can help distinguish layers of organic and aqueous solutions in the laboratory.

Puzzle 6.1 ———

Which has the higher boiling point, 1-chlorobutane or 2-chloro-2-methylpropane? Explain in terms of intermolecular forces.

Puzzle 6.2 ———

(a) Chlorofluorocarbons (CFC's) have been implicated in the depletion of the ozone layer in the stratosphere. Before being banned by many countries, CFC's were used as refrigerants and aerosol propellants, which need relatively low boiling points. Which CFC has the higher boiling point, trichlorofluoromethane (Freon 11) or dichlorodifluoromethane (Freon 12)? Explain.
(b) Replacements for CFC's must also have low boiling points. Which possible replacement has the higher boiling point, 1,1-dichloro-2,2,2-trifluoroethane or 1,1,1,2-tetrafluoroethane? Explain.

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6.3 Mechanism of S_N2 Reactions

It is time for our first type of organic reaction. Only a clear picture of the mechanism allows real understanding of a reaction. The mechanism of our first organic reaction is revealed by two kinds of studies: kinetic and stereochemical.

6.3A Kinetics of S_N2 Reactions

As noted in Chapter 5, kinetic studies commonly provide information about mechanisms. Consider the reaction:

$$\begin{array}{ccccccc} CH_3 & & & \text{propanone} & CH_3 & & \\ | & & & & | & & \\ CH_3CH_2\text{-CH-Br} & + & HO^- & \xrightarrow{\hspace{2cm}} & CH_3CH_2\text{-CH-OH} & + & Br^- \\ \\ \text{2-bromobutane} & & & & \text{2-butanol} & & \end{array}$$

Here an alkyl bromide produces its corresponding alcohol in propanone (acetone) solvent. The reaction rate is found to be directly proportional to both reactant concentrations. Thus the rate equation takes this form:

$$rate = k[\text{R-Br}][\text{HO}^-]$$

The reaction is first order in each reactant. Evidently, both reactants react in (or possibly before) the rate-limiting step. This fact is most easily explained by a concerted reaction with a one-step mechanism, where the one step brings both reactants together. This is called a **bimolecular** reaction because two molecules react in the rate-limiting step.


Puzzle 6.3 ──

(a) How would tripling the concentrations of both reactants affect the rate of the above reaction?
(b) How would halving the concentrations of both reactants affect the rate of the above reaction?

6.3B Stereochemistry of S_N2 Reactions

To learn more about reaction mechanisms, a second aspect of reactions is often studied: stereochemistry. A useful stereochemical experiment identifies the stereoisomer produced from a particular reactant stereoisomer. Note that the 2-bromobutane reactant and the 2-butanol product both contain chiral atoms and so exist as R and S enantiomers (Section 3.2A). If only the R enantiomer of 2-bromobutane is used for reaction, only the S enantiomer of 2-butanol, and none of the R enantiomer, is found as product.

Which one-step mechanism is consistent with this stereochemical evidence? Let us consider two approaches by which the hydroxide ion might displace the bromine from 2-bromobutane. The first approach is frontal:

(R)-2-bromobutane   (R)-2-butanol
            retention of configuration by frontal approach
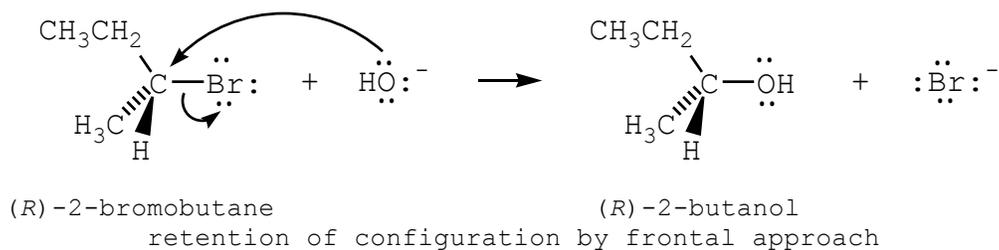
Such a frontal approach, where the nucleophile displaces the departing bromine on the same side of the electrophile, would retain the configuration at the chiral atom. Thus, the R enantiomer of 2-butanol would result, not the actual S product. Evidently the reaction does not proceed by frontal approach.

Alternatively, the nucleophile might arrive at the back:

(R)-2-bromobutane   (S)-2-butanol
            inversion of configuration by back approach
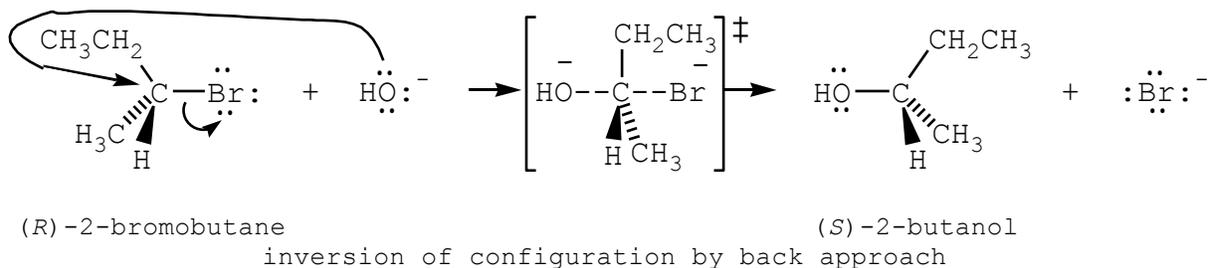
By engaging the back of the carbon holding the leaving atom, a nucleophilic lone pair of the hydroxide ion not only expels the bromine with its bonding electrons, but also repels the bonding electrons of the hydrogen, ethyl, and methyl groups on the reacting carbon. In the transition state the reacting carbon has become trigonal bipyramidal. Its bonds to the hydrogen, ethyl, and methyl groups lie in one plane, while the hydroxide and bromine sit at the apexes of the pyramids. In the product the chiral atom has returned to sp^3 hybridization and its configuration has been inverted. Thus, (S)-2-butanol is produced by this mechanism, in agreement with the experiment. Other similar experiments have indicated that this kind of reaction always proceeds by such a one-step mechanism, where the nucleophile engages the back of the electrophile's carbon to invert its configuration.

This mechanism is called **S$_N$2.** S$_N$2 stands for substitution, nucleophilic, bimolecular. It is bimolecular because both reactants participate in the rate-limiting step. It is a nucleophilic substitution because a nucleophile replaces a leaving group on the electrophile. Figure 6.1 displays the energy-reaction diagram for the above S$_N$2 reaction.
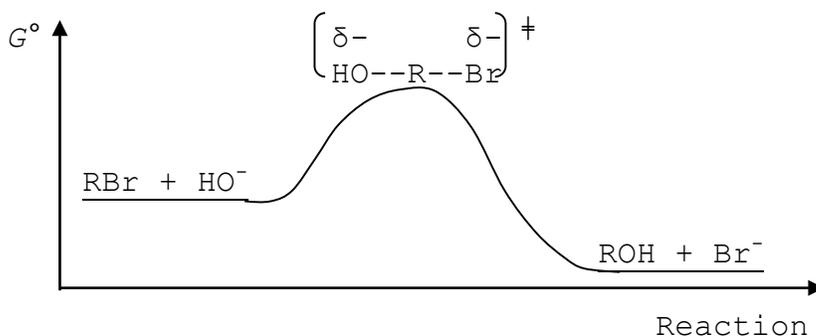
Figure 6.1 The energy-reaction diagram for the S$_N$2 reaction of (R)-2-bromobutane with hydroxide ion.

Note the single transition state and the absence of any intermediate for the one-step mechanism.

The S$_N$2 reaction featured in this section exemplifies a completely **stereoselective reaction**. A stereoselective reaction does not give equal amounts of all possible stereoisomer products, but preferentially selects one (or sometimes more) stereoisomer product at the expense of another possible stereoisomer. By requiring the nucleophile at the back of the electrophilic carbon, the S$_N$2 reaction above produces only (S)-2-butanol from (R)-2-bromobutane. No (R)-2-butanol forms.

Puzzle 6.4 ───

Consider the S$_N$2 reaction of (S)-2-bromobutane and hydroxide ion.
(a) Draw the mechanism with electron arrows. Include the three-dimensional structures of organic reactant, transition state, and organic product(s).
(b) Name the organic product(s).
(c) How would the energy-reaction diagram for this reaction differ from Figure 6.1?

6.4 Effective Reactants for S_N2 Reactions

S_N2 reactions are common and important in organic chemistry. Yet they do not occur between any nucleophile and electrophile. According to Section 4.10, nucleophiles and electrophiles in general have some selectivity. For example, a weak nucleophile reacts only with a strong, reactive electrophile. In the case of S_N2 reactions, we would also expect selectivity among reactants. So which reactants succeed in S_N2 reactions?
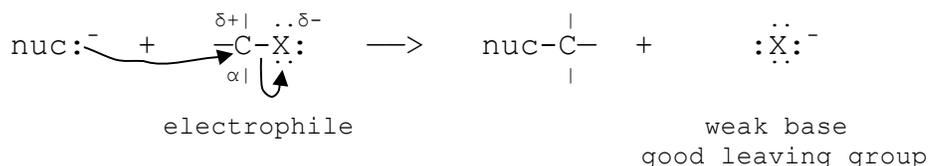
6.4A Leaving Groups of S_N2 Electrophiles

Let us first consider our usual type of electrophile for an S_N2 reaction. It is an alkyl halide, such as the one in our first example above, 2-bromobutane. Other types of electrophiles react in S_N2 reactions and will be considered in Section 10.5C.

Why are many alkyl halides suitable electrophiles for S_N2 reactions? One essential feature is the halogen atom itself. To understand the two ways by which this halogen facilitates an S_N2 reaction, consider a general S_N2 reaction with an alkyl halide:

```
                    δ+|  ..δ-                    |
nuc:⁻    +        ⸺C–X:      ⟶    nuc–C–   +        :X:⁻
                    α|  ..                         |    ..

        electrophile                        weak base
                                         good leaving group
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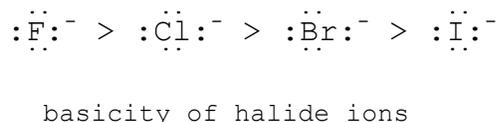
More electronegative than carbon, the halogen puts a partial positive charge on the carbon bonded to it. Thus, this so-called **α carbon** is an electrophilic atom, attracting an electron-rich nucleophile.

The halogen makes an alkyl halide an electrophile in another way. When leaving the electrophile, the halogen accepts the electron pair from its bond to carbon as an additional lone pair. Such an atom (or group of atoms) that departs from its parent molecule with an electron pair is called a **leaving group,** abbreviated L. According to Section 5.2, reactions tend to yield more stable products more readily. An inverted measure of a leaving group's stability is its basicity.

as basicity of L ↓, stability of L ↑ & S_N2 rate ↑

Note that we consider the leaving group as a *product*, not as part of the electrophile. Having already acquired a new lone pair, it is a base. In general, *a suitable leaving group for an S_N2 reaction is a weak base*, that is, it has a strong conjugate acid ($K_a > 10^{-7}$). In other words, if H-L is a strong acid, R-L has a good leaving group for an S_N2 reaction. Once again we observe the similarity between the chemistries of hydrogen and carbon.

In fact, all of the halide ions are weak bases and so qualify as good leaving groups. But which halide ion is the best leaving group? We know from Section 4.9A:

$$:\overset{..}{\underset{..}{F}}:^- \; > \; :\overset{..}{\underset{..}{Cl}}:^- \; > \; :\overset{..}{\underset{..}{Br}}:^- \; > \; :\overset{..}{\underset{..}{I}}:^-$$

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        basicity of halide ions
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because increasing size softens and weakens the base electron pairs. Their ranking as leaving groups is then inverted:

$$:\overset{..}{\underset{..}{I}}:^- \; > \; :\overset{..}{\underset{..}{Br}}:^- \; > \; :\overset{..}{\underset{..}{Cl}}:^- \; > \; :\overset{..}{\underset{..}{F}}:^-$$

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ability as leaving group in S_N2 reaction
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Although iodide ion is the best halide leaving group, alkyl iodides are more expensive, harder to make, and less available than the other alkyl halides. Consequently, the most common alkyl halides for S_N2 reactions and other reactions are alkyl chlorides and alkyl bromides.

Puzzle 6.5 ――

Which of the following are good S_N2 leaving groups? Use Table 4.1, as needed.
(a) $CH_3CO_2^-$ (b) HO^- c) H_2O (d) $N{\equiv}C^-$ (e) H^- (f) H_3C^- (g) H_3N

Puzzle 6.6 ――

Lactose, the sugar in milk, is biosynthesized from two smaller sugars perhaps by an S_N2 reaction:


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  UDP-galactose        glucose                        UDP
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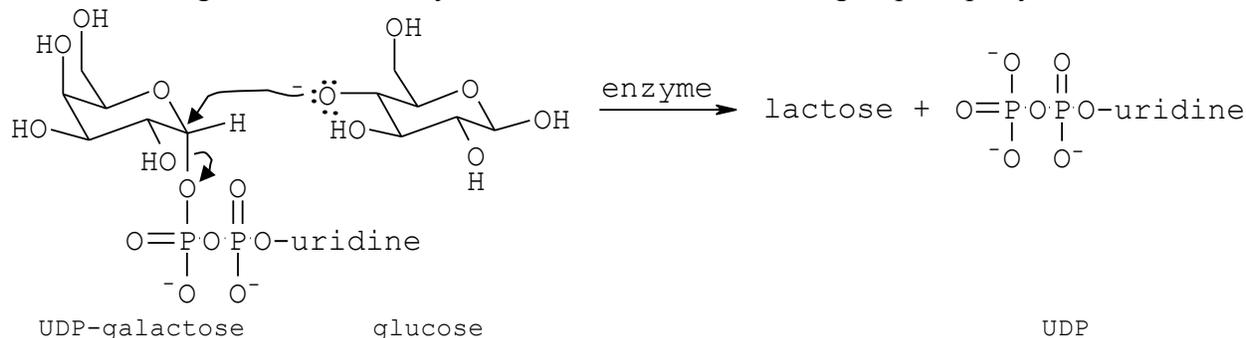
(a) Assuming an S_N2 reaction, draw lactose with proper stereochemistry.
(b) Is the UDP (i.e., uridine diphosphate) product a good leaving group? Its conjugate acid has a K_a of 10^{-6}.

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6.4B Carbon Skeletons of S_N2 Electrophiles

In addition to the leaving group, a second structural feature affects the ability of an electrophile to react in an S_N2 reaction: its **carbon skeleton,** that is, its interconnected carbon structure. Consider Table 6.1. The α carbon is the carbon attached to a halogen. The table indicates that methylation of the α carbon dramatically slows the S_N2 reaction for a given halogen. Indeed, the tertiary halide, with three α methyl groups, practically does not react in S_N2 reactions.

Table 6.1 Effect of α Methylation of an Alkyl Halide on S_N2
Reaction Rates

R-X	α CH_3-X	α CH_3CH_2-X	α $(CH_3)_2CH-X$	α $(CH_3)_3C-X$
Class	Methyl	1°	2°	3°
Relative Rate	30	1	0.02	~0

How does methylation at the α carbon slow an S_N2 reaction? Let us compare the structures of a methyl halide and a *tert*-butyl halide. The stereoselective S_N2 reaction requires the nucleophile to seek the back of the α carbon. Because of their small size, the three hydrogens at the back of a methyl halide's α carbon only slightly hinder the approach of a nucleophile:
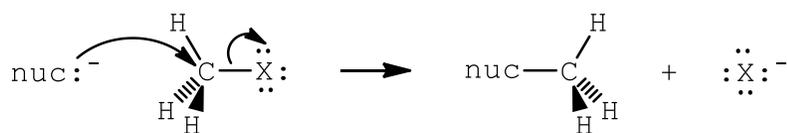
methyl halide

sterically open nucleophilic encounter with a methyl halide

In contrast, a *tert*-butyl halide's three methyl groups, much larger than hydrogens, greatly hinder the approach of a nucleophile:
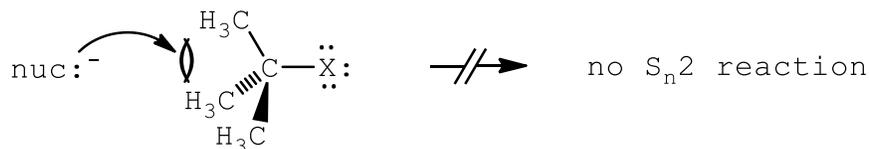
tert-butyl halide

sterically hindered nucleophilic encounter with a *tertiary*-butyl halide

These three alkyl groups prevent S_N2 reaction by a phenomenon called **steric** (i.e., spatial) **hindrance.** Like the repulsion of eclipsed bonds (Section 2.6A), steric hindrance results from electron repulsion. When attached to the α carbon, alkyl groups of any size sterically hinder a back approach and slow the S_N2 reaction. Thus:

methyl > 1° > 2°; not 3°

suitability of alkyl halides for S_N2 reaction

The steric hindrance of its three α alkyl groups generally prevents a tertiary halide from reacting in an S_N2 reaction.

Does alkylation of a β carbon, a carbon next to the α carbon, also sterically hinder S_N2 reactions? Consider Table 6.2. Note that each alkyl halide is primary, because the class reflects

the number of alkyl groups on the α, not the β, carbon. Clearly, methylation of the β carbon slows the S$_N$2 reaction. Evidently, alkylation of a β carbon increases steric hindrance at the α carbon.

Table 6.2 Effect of β Methylation of an Alkyl Halide on S$_N$2 Reaction Rates

R-X	β α CH$_3$CH$_2$X	β α CH$_3$CH$_2$CH$_2$X	β α (CH$_3$)$_2$CHCH$_2$X	β α (CH$_3$)$_3$CCH$_2$X
Class	1°	1°	1°	1°
Relative Rate	1	0.4	0.03	~0

Yet, Tables 6.1 and 6.2 show that β alkylation hinders an S$_N$2 reaction less dramatically than α alkylation. Each methylation of a β carbon reduces the reaction rate by a smaller factor than does methylation of an α carbon. Because the β carbon is more remote from the route of nucleophilic approach, the β carbon must be quaternary to effectively prevent S$_N$2 reaction by steric hindrance. An example is the so-called neopentyl skeleton:

neopentyl halide
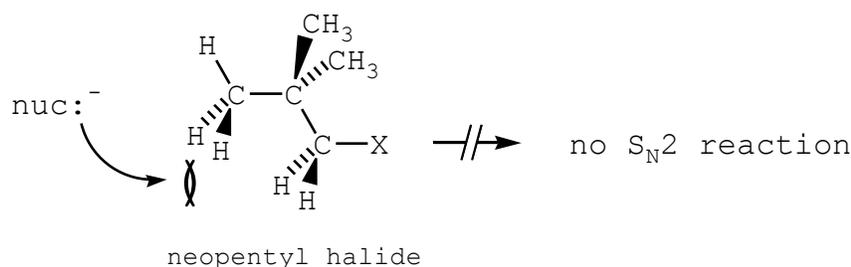
Because alkylation of a β carbon is rarely so complete that it prevents S$_N$2 reaction, we usually only consider the degree of α alkylation when assessing the carbon skeleton for possible S$_N$2 reaction. The *number* of alkyl groups on the α carbon is more important than the *size* of these alkyl groups. For example, two methyl groups (relative rate of 0.02 in Table 6.1) sterically hinder the nucleophile 20 times more than does one ethyl group (relative rate of 0.4 in Table 6.2).

Puzzle 6.7 ───

Indicate which of the following are suitable S$_N$2 electrophiles. Explain.
(a) CH$_3$I (b) (CH$_3$)$_2$CHOH (c) CH$_4$ (d) CH$_3$CH$_2$CH$_2$CH$_2$CH$_2$Br (e) CH$_3$CH$_3$
(f) (CH$_3$)$_2$CHC≡N (g) CH$_3$CH$_2$CHClCH$_3$ (h) (CH$_3$CH$_2$)$_3$CBr (i) (CH$_3$)$_2$CHOCH$_3$
(j) (CH$_3$)$_3$CH

Puzzle 6.8 ───

The electrophile *S*-adenosylmethionine methylates various biological nucleophiles in S$_N$2 reactions. For example, it methylates an amine to give epinephrine (i.e., adrenaline), a hormone instrumental in smooth muscle contraction and heart function.

S-adenosylmethionine   epinephrine
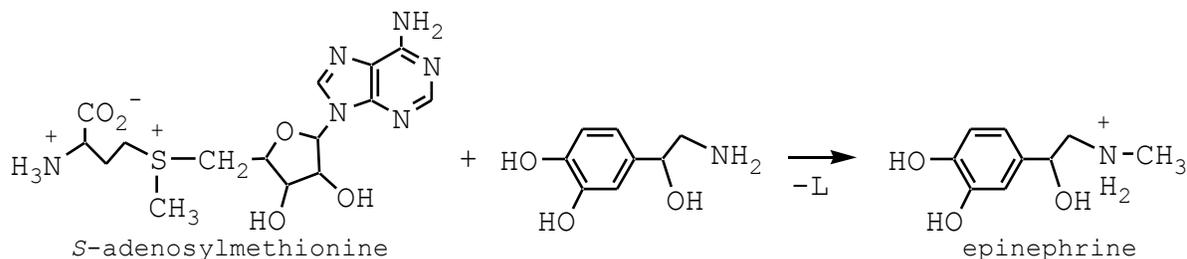
(a) Draw the leaving group, L, and explain why it serves as a good leaving group. K_a of $H_2S =$ 1×10^{-7}.

(b) What electrophilic advantage does the methyl group in *S*-adenosylmethionine have over the other two carbons α to the sulfur?

(c) Draw the electron arrows for this reaction.

6.4C Nucleophiles for S_N2 Reactions

To assess the suitability of a nucleophile for an S_N2 reaction, we must ask two general questions about the electrophilic alkyl halide. The most important question comes first. Is it a strong electrophile (Section 4.11)? An alkyl halide has neither a big positive charge nor unfilled orbitals on any of its atoms. Thus, simple alkyl halides are weak electrophiles. Accordingly they only react with strong nucleophiles.

Secondly, we ask if alkyl halide electrophiles are soft (Section 4.8). Their only positive charge is a partial one on the carbon singly bonded to a halogen, usually chlorine or bromine. Consequently, the partial charge is small, the α carbon has low charge den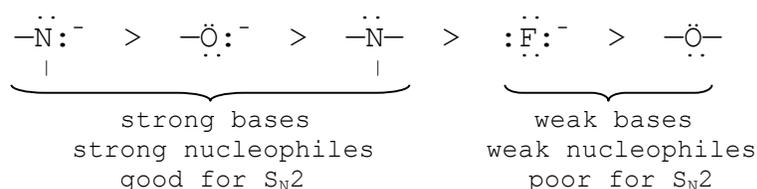sity, and an alkyl halide is a soft electrophile. This means that a soft nucleophile, even if weakly basic, may be nucleophilic enough to react with soft alkyl halides in an S_N2 reaction.

Now that we know the kinds of nucleophiles suitable for an S_N2 reaction, let us assess some common nucleophiles with nucleophilic atoms from the second row of the periodic table. According to Table 4.1, in basicity:


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strong bases              weak bases
strong nucleophiles     weak nucleophiles
  good for SN2            poor for SN2
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Because these nucleophiles all have nucleophilic atoms from one row of the periodic table, their order of basicity is roughly their order of nucleophilicity (Section 4.10). Accordingly the first nucleophile is not only the strongest base but also the strongest nucleophile. Furthermore, the first three nucleophiles all suit S_N2 reactions, whereas the last two are poor S_N2 nucleophiles.

Next let us assess three nucleophiles with nucleophilic atoms from lower rows of the periodic table. According to Table 4.1, chloride ion, bromide ion, and iodide ion are all weak bases (conjugate acids have K_a values $> 10^{-7}$). Yet these nucleophiles have large nucleophilic atoms. Thus, these are soft nucleophiles and are therefore strong nucleophiles when reacting with soft electrophiles, such as alkyl halides in S_N2 reactions. Unlike fluoride ion these three halide ions are good S_N2 nucleophiles. Here are important examples of weak bases whose softness makes them strong nucleophiles with soft electrophiles.

Beside the factors of basicity and softness, a last and least criterion for assessing the strength of an S_N2 nucleophile is steric bulk of the nucleophile *as a whole*. Note that the bulk does not refer to the size of the nucleophilic atom alone. We already know that increasing the size of the nucleophilic *atom* increases its softness and S_N2 reactivity. In contrast, large bulk in the nucleophilic *molecule* diminishes S_N2 reactivity. Consider two **alkoxide ions,** that is, alkyl oxide ions:

ethoxide ion
strong base
strong S$_N$2 nucleophile

tert-butoxide ion
strong base
weaker S$_N$2 nucleophile
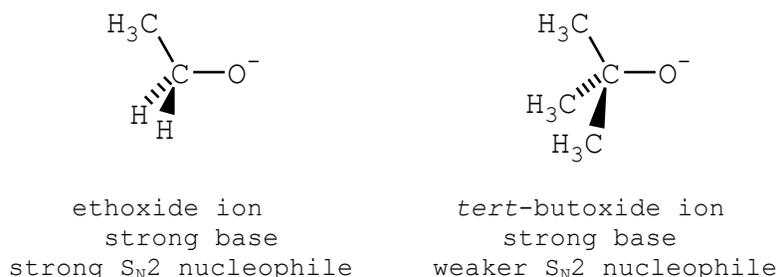
Both alkoxides are similarly strong bases, because steric bulk does not usually interfere with the plucking of a proton from the periphery of an acid. A base does not have to penetrate the interior of an acid, but an S_N2 nucleophile must penetrate to the interior α carbon of an alkyl halide. So, the large bulk of *tert*-butoxide ion reduces its nucleophilicity without reducing its basicity.

In other words, steric hindrance can result from either the electrophile (Section 6.4B) or the nucleophile. Yet, in general the steric bulk of the nucleophile must be large to reduce its S_N2 strength significantly, whereas each additional alkyl group on the α carbon of the electrophile substantially reduces its S_N2 capability.

To summarize Section 6.4C:

S_N2 rate ↑ as nucleophilic basicity ↑ & as nucleophilic softness ↑ & as overall nuc bulk ↓

A flow chart determines which bases are good S_N2 nucleophiles.

<u>poor S$_N$2 nuc.</u>

↑ no

| is it a strong base? | no ⟶ | is it a soft nuc.? | yes ⟶ | <u>good S$_N$2 nuc.</u> |

↓ yes

| is it *very* bulky? | no ⟶ | <u>good S$_N$2 nuc.</u> |

↓ yes
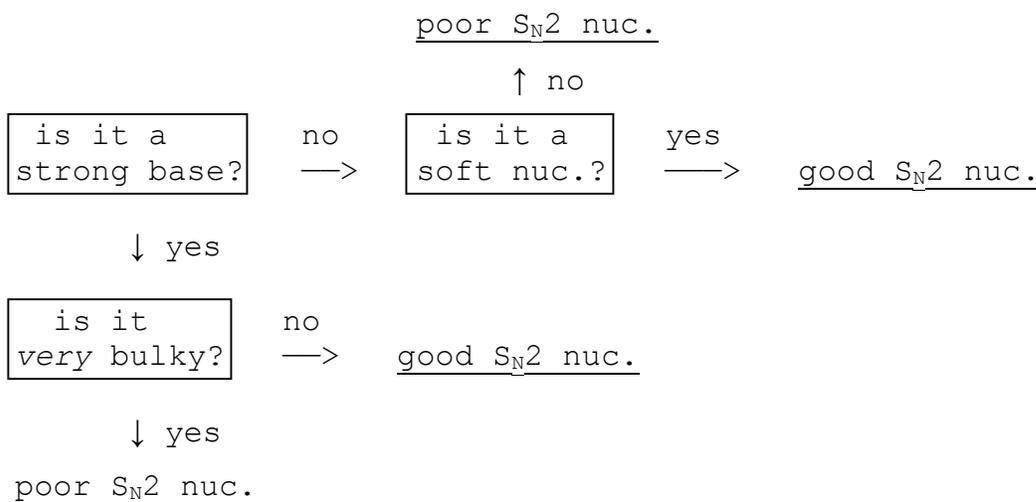
<u>poor S$_N$2 nuc.</u>

screening a base as an S$_N$2 nucleophile

Table 6.3 then summarizes all of Section 6.4.

Table 6.3   Effective Reactants for S_N2 Reactions

Electrophiles: R-L	Nucleophiles
Weakly basic L⁻ needed e.g., X⁻	Strong bases (not too bulky) e.g., —O⁻, —N—
Methyl > 1° > 2°; not 3°	*Soft*, weak bases (not too bulky) e.g., Cl⁻, Br⁻, I⁻

Puzzle 6.9 ──

Indicate which of the following are good S_N2 nucleophiles. Explain.
(a) CH_3O^- (b) CH_3NH_2 (c) CH_3OH (d) $N{\equiv}C^-$ (e) $CH_3CH_2S^-$ (f) $CH_3CO_2^-$
(g) $N(CH(CH_3)_2)_3$

Puzzle 6.10 ──

S-adenosylmethionine methylates a precursor to create epinephrine (Puzzle 6.8, Section 6.4B).

| *S*-adenosylmethionine | precursor | epinephrine |
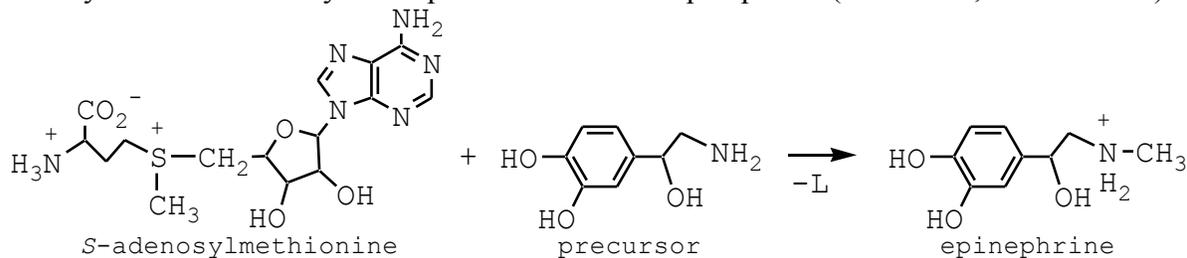
What nucleophilic advantage does the nitrogen of the precursor have over the precursor's oxygens?
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6.5 Mechanism of S_N1 Reactions

If either the alkyl halide or the nucleophile does not suit an S_N2 reaction, another kind of nucleophilic substitution reaction may still occur. Let us explore this alternative reaction.

6.5A General Characteristics of the S_N1 Mechanism

Consider the synthesis of a tertiary chloride from a tertiary bromide:

$$
\begin{array}{ccccccc}
 & CH_3 & & & & CH_3 & \\
 & | & & & & | & \\
CH_3-C-Br & & + & Cl^- & \longrightarrow & CH_3-C-Cl & + \quad Br^- \\
 & | & & & & | & \\
 & CH_3 & & & & CH_3 & \\
\end{array}
$$
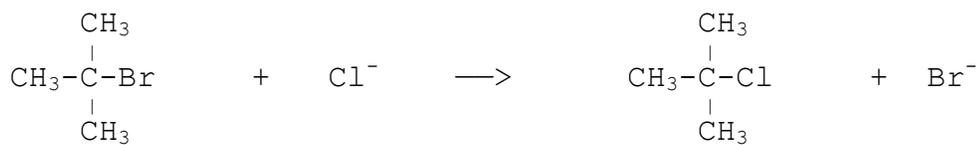
| 2-bromo-2-methylpropane | 2-chloro-2-methylpropane |

Clearly, this is a nucleophilic substitution because a nucleophile, Cl⁻, has replaced bromine on the

electrophile. But is it an S_N2 reaction? Its nucleophile is a weak but soft and not bulky base, and therefore a good, strong S_N2 nucleophile. Yet, this is not an S_N2 reaction because the electrophilic alkyl halide is tertiary and too bulky for S_N2 reaction.

What kind of nucleophilic substitution is this? Kinetic experiments provide an important insight, just as they did for S_N2 reactions (Section 6.3A). The rate for the above reaction is found to be first order in the alkyl halide and *zero order* in chloride ion! So the rate equation results:

$$\text{rate} = k[\text{R-Br}]$$

Evidently, the nucleophilic chloride ion is not reacting in the rate-limiting step, in contrast to the nucleophile's role in the S_N2 reaction (Section 6.3A). Only the electrophilic alkyl halide reacts in the slow step of the present reaction. Thus the reaction is unimolecular, unlike the bimolecular S_N2 reaction. It has a so-called **S_N1** mechanism: *unimolecular* nucleophilic substitution. Note that the *1* refers to the number of molecules reacting in the rate-limiting step, not the number of steps in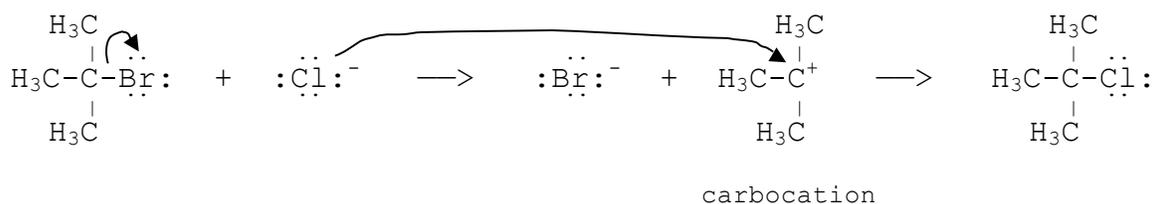 the mechanism. There must be at least two steps because the rate-limiting step does not use both reactants. The S_N1 mechanism for the above reaction actually has two steps:

carbocation

Here is the energy-reaction diagram for this reaction:
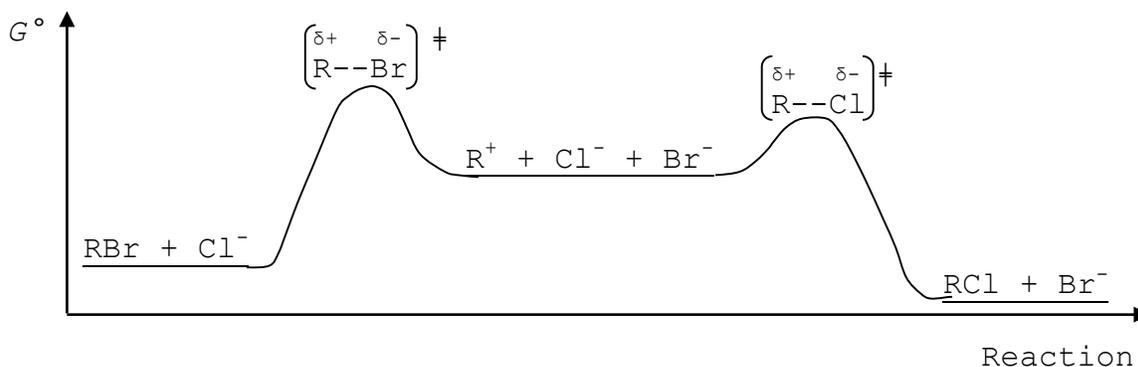
energy-reaction diagram for an S_N1 reaction

Note the two transition states and the intermediate stage, indicative of a two-step mechanism. Let us examine each step of this S_N1 mechanism.

Puzzle 6.11 ──

(a) How would doubling the concentration of $(CH_3)_3CBr$ affect the rate of the above S_N1 reaction?
(b) How would doubling the concentration of chloride ion affect the rate of the above reaction?

6.5B The First Step of the S_N1 Mechanism

According to the rate equation for this reaction, which is the slow, rate-limiting step? It must be the first step, which, like the rate equation, involves the alkyl halide but not the chloride ion. The slowness of the first step is not surprising because it requires energy to break a bond, without any bond formation to compensate.

What kind of leaving group does an S_N1 reaction demand? Like the S_N2 reaction *the S_N1 reaction requires a weakly basic leaving group*. The reasoning is similar. The rate-limiting step delivers an electron pair onto the leaving group as a lone pair.

as basicity of L ↓, stability of L ↑ & rls rate ↑ & S_N1 rate ↑

Accordingly, the weakly basic halide ion leaving group of any alkyl halide suits an S_N1 reaction. Furthermore, the ranking of halide leaving groups exactly parallels their ranking in S_N2 reactions (Section 6.4A):

$$F^- \quad < \quad Cl^- \quad < \quad Br^- \quad < \quad I^-$$

```
ability as leaving group in SN1 or SN2 reaction
```

Next consider the other structural feature of the electrophile, the carbon skeleton. Table 6.4 shows how the carbon skeleton affects the rate of S_N1 reactions. The table indicates that methylation of the α carbon dramatically accelerates the S_N1 reaction. In general:

$$3° \quad > \quad 2°; \quad \text{not } 1° \text{ or methyl}$$

```
suitability of alkyl halides for SN1 reactions
```

Neither methyl nor primary halides are normally S_N1 electrophiles. Note that this order of reactivity inverts the trend for S_N2 reactions, where methyl and primary halides are ideal electrophiles and tertiary halides do not react!

```
Table 6.4  Effect of α Methylation of an Alkyl Halide on SN1
Reaction Rates
```

R-X	α CH_3-X	α CH_3CH_2-X	α $(CH_3)_2CH-X$	α $(CH_3)_3C-X$
Class	Methyl	1°	2°	3°
Relative Rate	~0	~0	1	10^5

How does α methylation (or other α alkylation) of an alkyl halide quicken S_N1 reactions? Let us examine the organic intermediate produced in the rate-limiting, first step: the carbocation. *The carbocation is the key factor in an S_N1 reaction that determines many of the reaction's properties*. Consider four classes of carbocations:

$$\overset{+}{C}H_3 \qquad R-\overset{+}{C}H_2 \qquad \underset{\overset{|}{R'}}{R-\overset{+}{C}H} \qquad \underset{\overset{|}{R'}}{R-\overset{+}{C}-R''}$$

methyl   1°   2°   3°
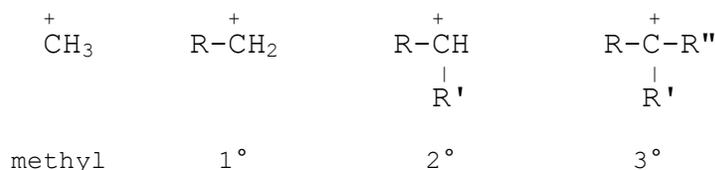
As it does for alkyl halides and alcohols, the class depends on the number of alkyl groups attached to the carbon of the functional group. Accordingly, the intermediate carbocation of the S_N1 reaction of Section 6.5A is tertiary. This is not surprising because it derives from a tertiary halide. With three σ bonds and no lone pairs, cationic carbons are hybridized sp^2 with an empty p orbital perpendicular to the plane of the three σ bonds. Only six valence electrons surround the cationic carbon. Consequently, the octet-poor cationic carbon is a very strong electrophile.

Yet not all carbocations are equally unstable. Let us examine more closely a generic primary carbocation:

hyperconjugation of a carbocation

π bond
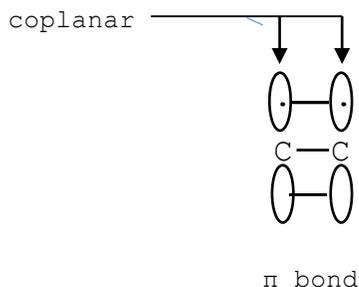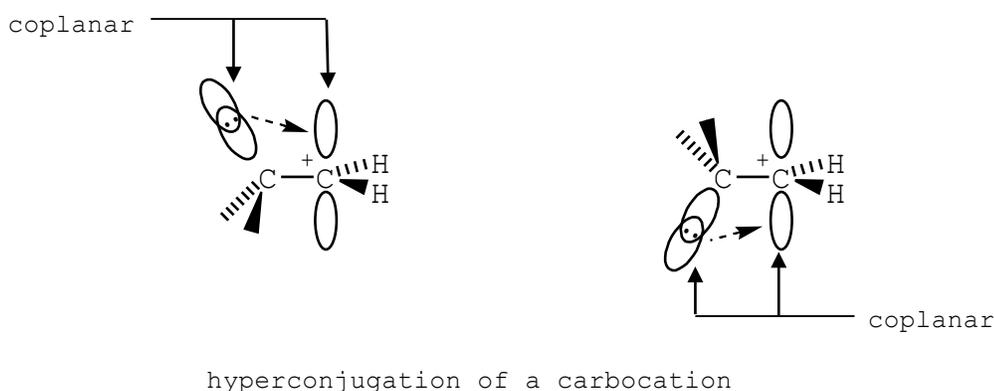
During rotation around the above carbon-carbon σ bond, one of the three further σ bonds on the β carbon often lies coplanar with the empty p orbital of the cationic carbon. In the two conformations above, either the upper or the lower lobe of the empty p orbital is coplanar with a σ bond on the β carbon. As a result, this σ bond can partially shift its electron density toward the near lobe of the empty p orbital. Although not a true bond, this sharing of electrons is like a very weak π bond with sideways overlap of adjacent orbitals. Thus, the cationic carbon is slightly stabilized by the attached alkyl group. This weak stabilization of a p orbital by an adjacent, coplanar σ bond is called **hyperconjugation.** Any alkyl group on the cationic carbon, no matter the size, can participate in hyperconjugation.

Neither hydrogen on the above cationic carbon can hyperconjugate because neither has the extra σ bonds of an alkyl group to share electron density. Therefore, as the number of alkyl groups on the cationic carbon increases, hyperconjugation and the stability of the carbocation increase.

Because more stable products are generally more easily formed:

$$3° \; > \; 2° \; > \; 1° \; > \; methyl$$

stability and ease of formation of carbocations

Indeed, *insufficient hyperconjugation normally prevents the formation of ordinary methyl or primary carbocations*. Thus, a tertiary halide reacts fastest by S_N1 reactions because it yields the most stable kind of carbocation, a tertiary carbocation, in its rate-limiting step. Ordinary methyl and primary halides do not react by S_N1 reactions because they do not produce the very unstable methyl and primary carbocations.

Puzzle 6.12 ───

Which of the molecules and ions in Puzzle 6.5 (Section 6.4A) are good S_N1 leaving groups?

Puzzle 6.13 ───

Indicate which of the compounds in Puzzle 6.7 (Section 6.4B) are suitable S_N1 electrophiles. Explain.

───

6.5C The Second Step of the S_N1 Mechanism

The rate equation tells us that the second step of an S_N1 reaction is not the slow, rate-limiting step. This is not surprising because a carbocation, even a tertiary one, with its octet-poor, positively charged carbon is a very strong electrophile. So, it rapidly bonds to a nucleophile and releases energy.

What kind of nucleophile is required? Because the nucleophile reacts with a very strong electrophile, the nucleophile can be weak or strong. In the S_N1 reaction of Section 6.5A, chloride ion was a strong nucleophile. Yet, the weak nucleophile, water, can also react in an S_N1 reaction while also serving as solvent:
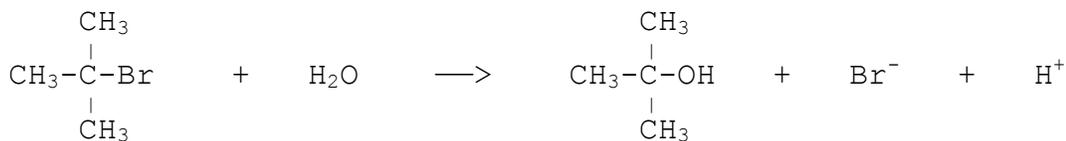
```
        CH₃                              CH₃
         |                                |
   CH₃-C-Br      +    H₂O    ⟶     CH₃-C-OH    +    Br⁻    +    H⁺
         |                                |
        CH₃                              CH₃

  2-bromo-2-methylpropane           2-methyl-2-propanol
```

This cannot be an S_N2 reaction because water is a weak nucleophile and the electrophile is tertiary. Instead the mechanism is S_N1:

$$(CH_3)_3C-\ddot{Br}: \quad \longrightarrow \quad :\ddot{Br}:^- \quad + \quad (CH_3)_3\overset{+}{C} \quad \overset{H_2\ddot{O}:}{\longrightarrow} \quad (CH_3)_3C-\overset{+}{\underset{|}{\ddot{O}}H}$$

$$\underset{H}{|}$$

3° halide   3° carbocation   oxonium ion

$$\big\downarrow\big\uparrow \; H_2\ddot{O}:$$

$$(CH_3)_3C-\ddot{O}H \quad + \quad H_3\ddot{O}^+$$
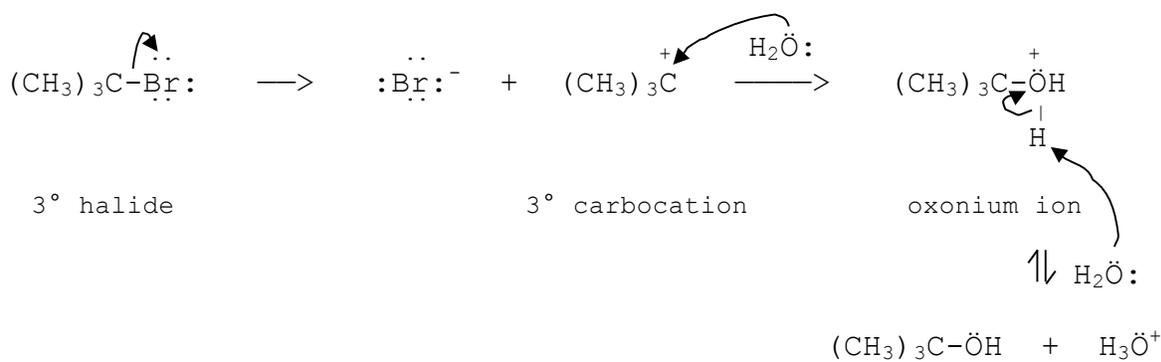
In the last step solvent water plucks a proton from the **oxonium ion** (i.e., an ion with a trivalent, cationic oxygen) to give a more stable, uncharged alcohol. Formally this step is an equilibrium with similarly weak bases on both sides (H_2O vs. $(CH_3)_3COH$), but the high concentration of solvent water base pushes the equilibrium forward, according to Le Châtelier's Principle (Henri-L. Le Châtelier, France, 1850-1936). Such an S_N1 reaction where solvent serves as the nucleophile is called a **solvolysis** reaction. Other solvents that react in S_N1 solvolysis reactions are alcohols. Like water, alcohols are weak nucleophiles and **protic solvents**. By definition protic solvents can donate a hydrogen bond to a suitable acceptor. In the last step of an S_N1 solvolysis, they can also lose a proton. Note that water loses a proton after forming an oxonium ion in the S_N1 solvolysis above.

Although practically any nucleophile, weak or strong, can react by an S_N1 mechanism, weak nucleophiles favor S_N1 over competing S_N2 reactions, which need strong nucleophiles (Section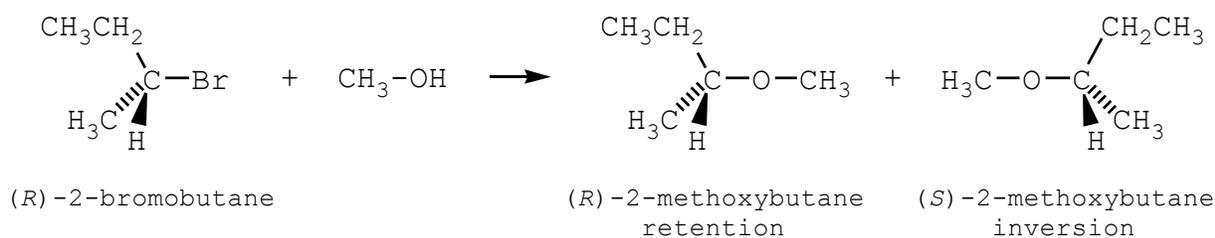 6.4C). Nucleophiles that are weak bases also assist S_N1 reactions by avoiding a competing reaction to be studied in the next chapter (Section 7.3).

Are S_N1 reactions stereoselective like S_N2 reactions (Section 6.3B)? By requiring the nucleophile to seek the back of the electrophile, an S_N2 reaction produces only one of two possible stereoisomers when a chiral electrophilic atom reacts. For example, S_N2 reaction of hydroxide ion with (*R*)-2-bromobutane yields only (*S*)-2-butanol (Section 6.3B). Let us examine an S_N1 reaction that involves the chiral atom of (*R*)-2-bromobutane:

(*R*)-2-bromobutane   (*R*)-2-methoxybutane   (*S*)-2-methoxybutane
                                           retention   inversion

This solvolysis with an alcohol solvent yields both possible ether stereoisomers by both retention and inversion of configuration at the α carbon chiral atom. In other words, the products form a racemic mixture (Section 3.1C). Evidently this reaction, like other S_N1 reactions, is not stereoselective.

We can explain this lack of stereoselectivity by the structure of the intermediate:

carbocation   R oxonium ion   S oxonium ion
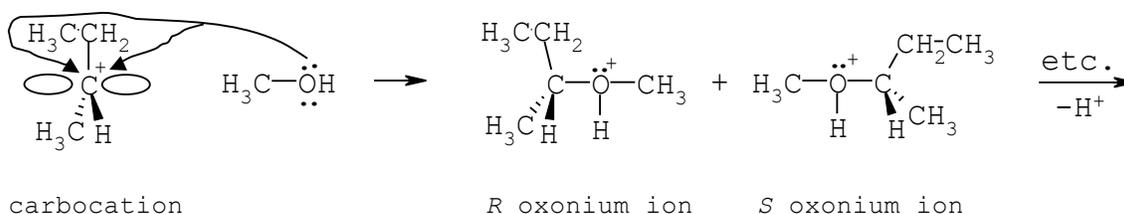
This planar, symmetrical carbocation is equally open to nucleophilic approach on either side of the plane of its sp^2 orbitals. Nucleophilic bonding to the right lobe of the empty p orbital produces the R oxonium ion and then the R ether. The S oxonium ion and ether result from reaction at the left lobe of the p orbital. Thus an optically inactive racemic product mixture results. This example illustrates the general principle that once optical activity is lost, as it is when (R)-2-bromobutane dissociates into a symmetrical carbocation, it cannot be regained without chiral reagents.

Puzzle 6.14 ——

Consider the reaction of (S)-2-bromobutane with ethanol.
(a) Is this mostly an S_N1 or S_N2 reaction? Explain.
(b) Draw the main mechanism with electron arrows. Include the three-dimensional structures of all organic compounds involved.

Puzzle 6.15 ——

Maltose, or malt sugar, sweetens malted milk and feeds yeast for brewing beer. It can be hydrolyzed into two glucose molecules in aqueous acid according to this mechanism:
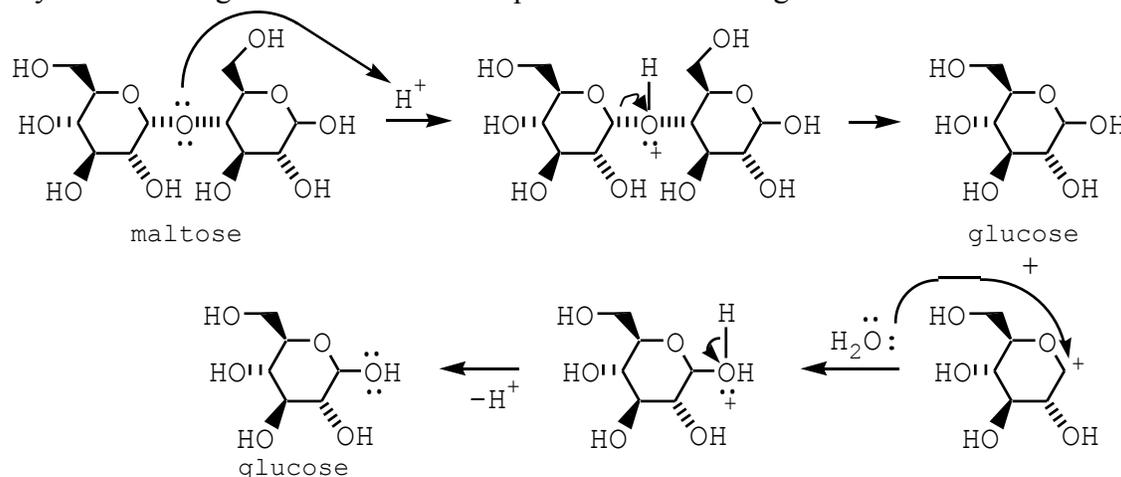
After the first step, an acid-base reaction, the reaction is S_N1 solvolysis.
(a) Assess glucose as the leaving group in the second step.
(b) Beside some hyperconjugation, what feature stabilizes the carbocation intermediate?
(c) Draw the two stereoisomers of glucose produced in the last step.

6.5D Carbocation Rearrangements in the S_N1 Mechanism

We have seen in the preceding section that solvolysis requires a third mechanistic step:

deprotonation of an oxonium ion. Another three-step S_N1 reaction leads to a surprising isomer product. Consider an alkyl halide interconversion (ignore its stereochemistry):

```
        H  Cl                              H  F                      F  H
        |  |                               |  |                      |  |
   CH3-C-CH-CH3   +   F⁻   ——→      CH3-C-CH-CH3   +    CH3-C-CH-CH3
        |                   -Cl⁻          |                      |
        CH3                               CH3                    CH3

    2-chloro-                          2-fluoro-            2-fluoro-2-methylbutane
      3-methylbutane                     3-methylbutane            rearranged
```
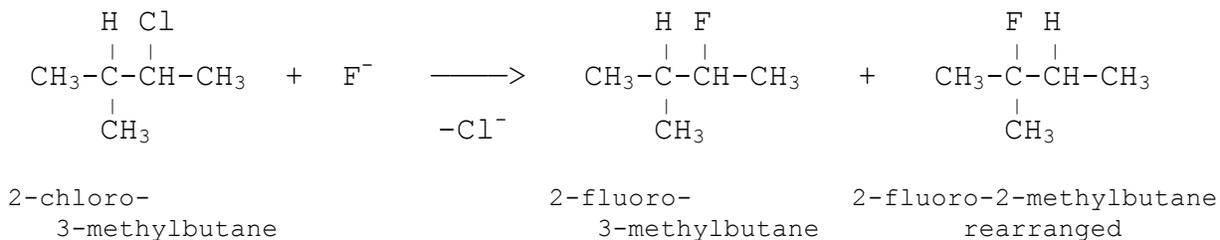
Is this nucleophilic substitution S_N1 or S_N2? The secondary halide could be either an S_N1 or S_N2 electrophile. The fluoride ion, however, is a weak, hard base and a weak nucleophile, unsuited for S_N2 reactions. So this is an S_N1 reaction. Whereas the first constitutional isomer product above is expected, the second isomer product is unexpected. Two concurrent mechanisms explain the isomers:

```
         .. ..                                    H              H  :F̈:
        H :Cl:                                     |  +           |  /
        | /↶                           :C̈l:⁻ + CH3-C-CH-CH3  ——→  CH3-C-CH-CH3
   CH3-C-CH-CH3 + :F:⁻  ——→   :Cl:⁻ +         |                       |
        |             ..                         CH3                     CH3
        CH3

                                                              first isomer
         ..
    ↓ -:Cl:⁻

                                                               ..
        H↶                H⁻ shift        H                  :F: H
        |  +                              +  |                |  /
   CH3-C-CH-CH3   ——————————→     CH3-C-CH-CH3   ——→   CH3-C-CH-CH3
        |                               |                       |
        CH3                             CH3                     CH3

    2° carbocation              3° carbocation           second isomer
```
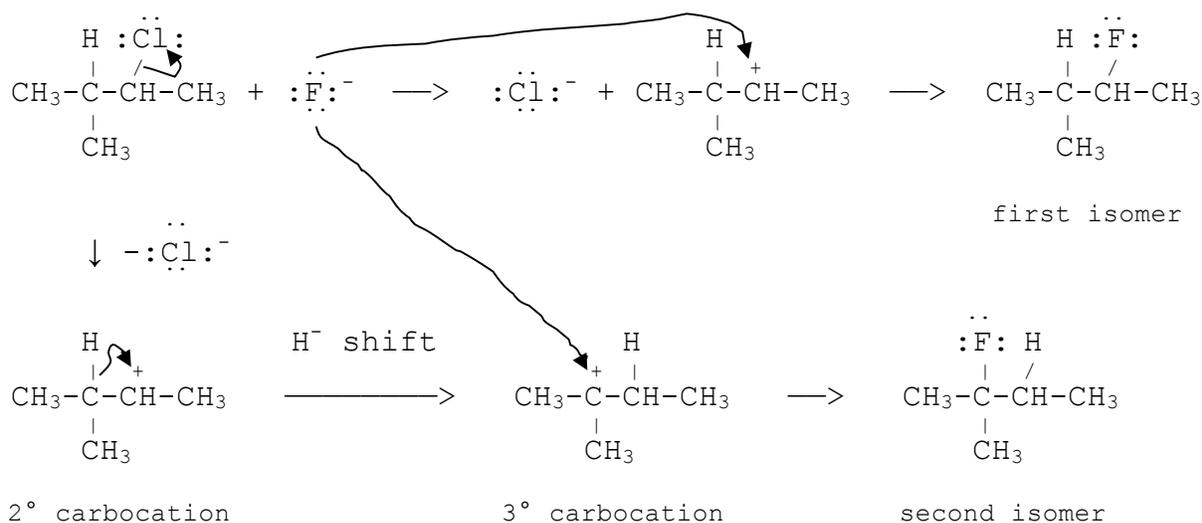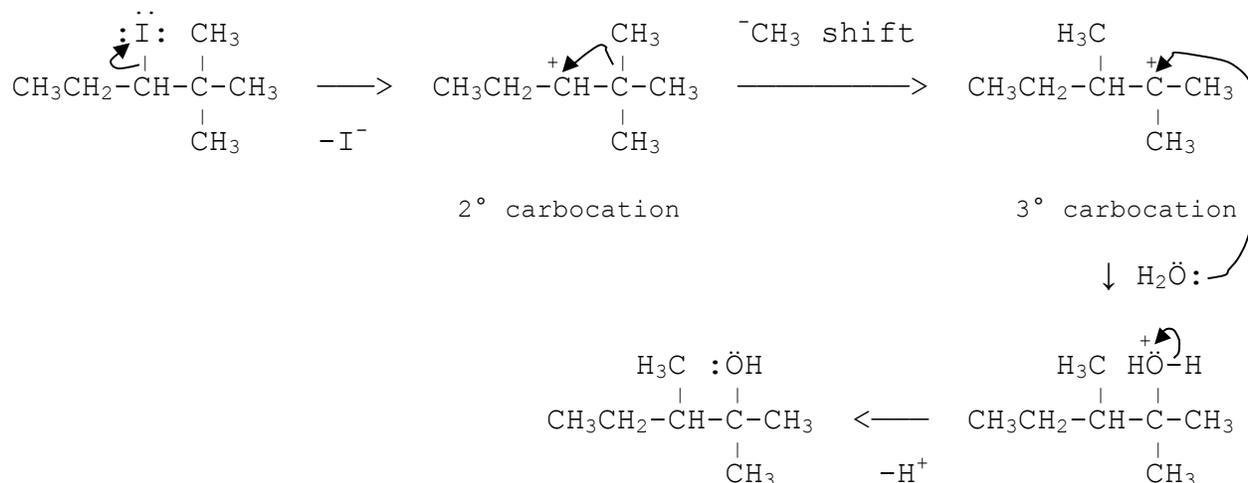
Note that in the second mechanism a hydrogen shifts with its bonding pair instead of leaving the electrons behind, as in an acid-base reaction. By moving with its bonding pair, the hydrogen shifts as a hydride anion, not as a proton. The hydride ion neutralizes the cationic carbon as it leaves behind a positive charge on the adjacent, abandoned carbon. A **carbocation rearrangement** results when one carbocation rearranges into another carbocation. Why does this rearrangement occur? A less stable secondary carbocation becomes a more stable tertiary carbocation. This is an exothermic, favorable step.

Usually a carbocation rearranges to form a more stable carbocation. Because simple primary carbocations are not normally formed, the usual rearrangement converts a secondary carbocation into a tertiary one. The rearrangement can occur by a shift of a hydride ion (not a proton), an alkyl (usually methyl) group or a phenyl group (Section 1.3B). A hydride shift is most common because it more likely leads to a more stable carbocation. The shifting atom or group always brings bonding electrons with it and shifts from a carbon adjacent to the cationic carbon, that is, from a β carbon. Both an unrearranged and a rearranged product result. Which isomer predominates depends on the relative rates of rearrangement and nucleophilic engagement. A strong nucleophile at high concentration diminishes rearrangement. Of course, carbocation

rearrangements cannot accompany S_N2 reactions, which do not generate carbocations.

Consider a carbocation rearrangement as an extension of hyperconjugation (Section 6.5B). The electron pair of an adjacent, coplanar σ bond goes completely to the carbocation, instead of hyperconjugation's *partial* sharing of an electron pair.

carbocation rearrangement

hyperconjugation of a carbocation

A second example illustrates a carbocation rearrangement with the shift of an alkyl group, not a hydride ion:

unrearranged   rearranged

This S_N1 reaction is a solvolysis, yielding two alcohol isomers. The mechanism for the second, rearranged product follows.

$$\underset{\substack{| \\ CH_3}}{CH_3CH_2-CH-\overset{CH_3}{\underset{|}{C}}-CH_3} \xrightarrow[-I^-]{} \underset{\substack{| \\ CH_3}}{CH_3CH_2-\overset{+}{C}H-\overset{CH_3}{\underset{|}{C}}-CH_3} \xrightarrow{^-CH_3 \text{ shift}} \underset{\substack{| \\ CH_3}}{CH_3CH_2-CH-\overset{H_3C}{\underset{|}{\overset{+}{C}}}-CH_3}$$

:Ï: CH₃

2° carbocation   3° carbocation

↓ H₂Ö:

$$\underset{\substack{| \\ CH_3}}{CH_3CH_2-CH-\overset{H_3C \quad :ÖH}{\underset{|}{C}}-CH_3} \xleftarrow[-H^+]{} \underset{\substack{| \\ CH_3}}{CH_3CH_2-CH-\overset{H_3C \quad HÖ-H}{\underset{|}{C}}-CH_3}$$

During the methyl shift a secondary carbocation rearranges to a more stable tertiary carbocation.

Puzzle 6.16 ───

Draw the mechanism with electron arrows leading to the rearranged product from the reaction of ethanol with 3-bromo-4-methylhexane.

Puzzle 6.17 ───

Steroids, including many hormones and cholesterol, have many functions in both plants and animals. During the biosynthesis of steroids, a carbocation intermediate undergoes a series of simultaneous rearrangements to yield another carbocation:
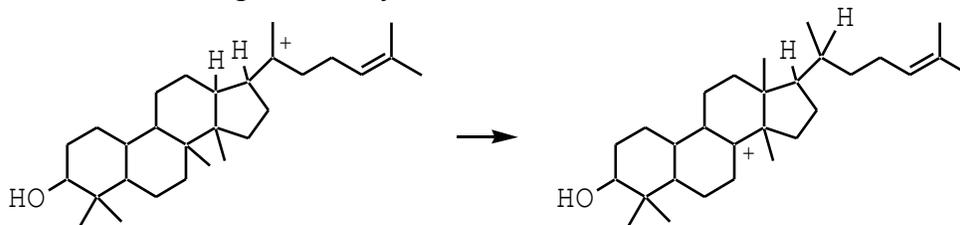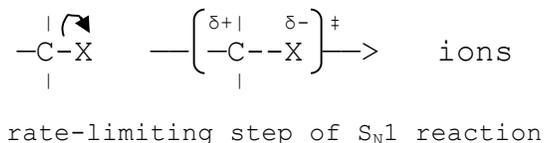
Draw the series of four rearrangements with electron arrows. (An enzyme facilitates this conversion of a tertiary carbocation to another tertiary carbocation.)

───

## 6.6 Preferred Solvents for S_N1 and S_N2 Reactions

How reasonable is the first step of an S_N1 reaction? This is the slow, rate-limiting step because a bond breaks without bond formation to compensate (Section 6.5B). A leaving group anion is separated from an oppositely charged carbocation. Consequently this is an endothermic, unfavorable process. Indeed, it may look hopeless until we recall from Section 1.11C how sodium hydroxide dissolves in water. There a bond was broken without compensating bond formation, and oppositely charged ions (sodium cation and hydroxide anion) were separated. That solution succeeded because of the many ion-dipole and hydrogen bond intermolecular forces between

product ions and protic solvent water molecules.

A similar situation arises in the first step of an S_N1 mechanism. An appropriate solvent must be present to assist the dissociation of alkyl halide. Consider the first, rate-limiting step with its transition state:

$$\begin{array}{c} | \\ -C-X \\ | \end{array} \quad \longrightarrow \left[\begin{array}{c} \delta+ \; | \quad \; \delta- \\ -C--X \\ | \end{array} \right]^{\ddagger} \longrightarrow \quad \texttt{ions}$$

```
            rate-limiting step of SN1 reaction
```

A protic solvent, such as water or a small alcohol (Section 6.5C), can begin to hydrogen bond with the incipient halide anion leaving group in the transition state:
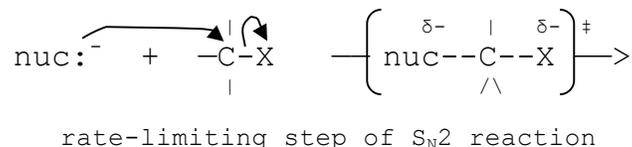
$$\left(\begin{array}{c} \delta+ \; | \quad \; \delta- \\ -C--X \\ | \quad \; | \\ \quad \; \delta+H-O-Sol \end{array} \right)^{\ddagger}$$
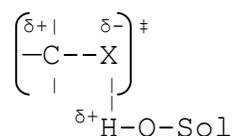
```
        incipient H bond stabilizing SN1 transition state
```

Such a hydrogen bond, even though not yet fully established, stabilizes the transition state of the rate-limiting step and thereby lowers the activation energy of the step. So not only this step but also the whole S_N1 reaction is expedited. Thus S_N1 reactions prefer protic solvents. Note that such protic solvents as water and alcohols are also nucleophiles and so are capable of S_N1 solvolysis reactions. They can do "triple duty": facilitate the first step by stabilizing the transition state, then serve as nucleophile in the second step, and finally serve as base by removing a proton from the oxonium ion in the third step.

The solvent preference of S_N2 reactions is not as general as in S_N1 reactions, but depends on the charge of the nucleophile. S_N2 reactions need strong nucleophiles, which are usually anions. Important exceptions include uncharged ammonia and amines (i.e., organic nitrogen compounds). Let us limit this discussion to S_N2 reactions with anionic nucleophiles, with the understanding that uncharged nucleophiles can alter the solvent preference.

As we did for the S_N1 reaction, let us compare the transition state to the reactants of the only step of an S_N2 reaction:

$$\texttt{nuc:}^{-} \;\; + \;\; \begin{array}{c} | \\ -C-X \\ | \end{array} \quad \longrightarrow \left[\begin{array}{c} \delta- \quad | \quad \delta- \\ nuc--C--X \\ /\backslash \end{array} \right]^{\ddagger} \longrightarrow$$

```
            rate-limiting step of SN2 reaction
```
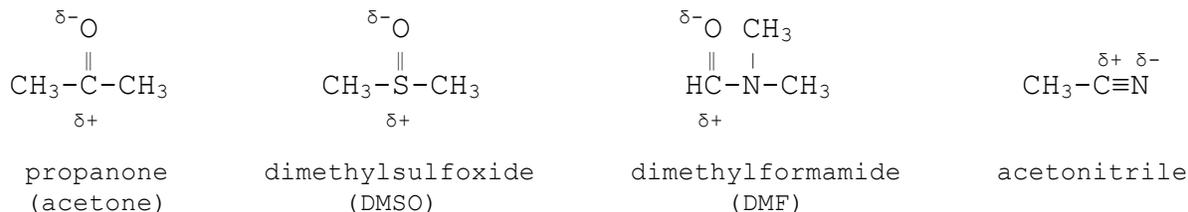
Although there is an incipient halide anion in the transition state, which can begin to hydrogen bond with protic solvent, the reactant nucleophile is a true anion. So a protic solvent molecule can fully hydrogen bond with a reactant molecule:

$$\texttt{nuc:}^{-}--\overset{\delta+}{H}-O-Sol$$
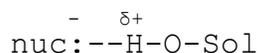
```
        H bond stabilizing SN2 reactant anion
```

Such solvation stabilizes the nucleophile more than it does the transition state. Therefore the activation energy is increased and the S_N2 reaction goes more slowly. In contrast, an aprotic solvent does not preferentially stabilize the nucleophile anion and does not slow the reaction. Consequently, S_N2 reactions using anionic nucleophiles prefer aprotic solvents. This is only a preference, however, and not a requirement. S_N2 reactions in protic solvents can also occur, but more slowly.
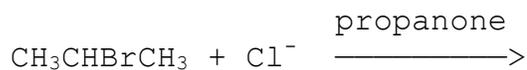
       Some examples of useful, aprotic solvents follow:

$$\overset{\delta-}{O} \qquad\qquad \overset{\delta-}{O} \qquad\qquad \overset{\delta-}{O}\ CH_3$$

$$\underset{\delta+}{CH_3-\overset{\|}{C}-CH_3} \qquad \underset{\delta+}{CH_3-\overset{\|}{S}-CH_3} \qquad \underset{\delta+}{H\overset{\|}{C}-\overset{|}{N}-CH_3} \qquad \overset{\delta+\ \delta-}{CH_3-C\equiv N}$$

```
   propanone        dimethylsulfoxide      dimethylformamide       acetonitrile
   (acetone)             (DMSO)                 (DMF)
```

Note that each has a polar double or triple bond, which magnifies the polarity.

Puzzle 6.18 ───

Consider the nucleophilic substitution:

$$CH_3CHBrCH_3 + Cl^- \xrightarrow{\text{propanone}}$$

(a) Is this mostly an S_N1 or S_N2 reaction? Explain.
(b) Draw the mechanism with electron arrows.

Puzzle 6.19 ───

A qualitative test for certain kinds of alkyl halides combines an ethanolic solution of silver nitrate with the sample to be tested.

$$Ag^+ + NO_3^- + R-X \xrightarrow{CH_3CH_2OH} AgX_{(s)} + \mathbf{A}$$
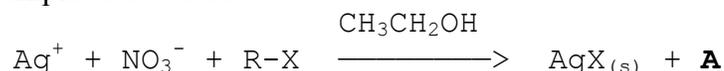
The silver halide is insoluble in ethanol, so a precipitate indicates a successful reaction.
(a) Is nitrate ion, NO_3^-, a suitable nucleophile for an S_N1 or S_N2 reaction? Explain.
(b) Is ethanol a suitable nucleophile for an S_N1 or S_N2 reaction? Explain.
(c) Is this an S_N1 or S_N2 reaction? Explain.
(d) Is ethanol a preferred solvent for this reaction? Explain.
(e) Which class of alkyl halide reacts fastest in this reaction?
(f) Which class(es) of alkyl halide react poorly in this reaction?
(g) Identify two possible kinds of product **A**.

───

6.7 Comparison of S_N1 and S_N2 Reactions

       We have learned a lot about nucleophilic substitutions, our first type of organic reaction. We did so by carefully examining S_N1 and S_N2 mechanisms, which result from the strengths, needs, and limitations of nucleophiles and electrophiles. Table 6.5 summarizes and compares the properties of our first two mechanisms. Despite giving similar products, S_N1 and S_N2 reactions

differ strongly in how they reach these products. It would be very difficult to remember all of this information without a clear vision of the S_N2 and S_N1 mechanisms and a sure sense of the structural features of reactants and intermediates. Do not just memorize this information, but understand how these properties result from molecular structure. In particular, note how many properties of an S_N1 reaction derive from its intermediate carbocation.

These properties apply to pure S_N1 and S_N2 reactions, which lie at opposite ends of a continuum of nucleophilic substitutions. Other reactions that lie along this continuum combine some of the properties of these two extremes. Their complexity does not warrant discussion in this text. Also, both S_N1 and S_N2 can occur in a reaction mixture with borderline properties.

Table 6.5   Summary of S_N2 and S_N1 Nucleophilic Substitutions

	S_N2	S_N1
Kinetics	1st order in 2 reactants both reactants in rls	1st order in elie only elie in rls
Number of steps	1 strong nuc doesn't wait	2 or more nuc awaits strong elie
Elie L group	Weak base needed e.g. X^- stable byproduct	Identical to S_N2
Elie C skeleton	$CH_3 > 1° > 2°$; not 3° minimize steric hindrance	$3° > 2°$; not 1° or CH_3 stabilize C^+
Nucleophile	Strong needed: strong base or soft nuc e.g. $-O^-$, $-N\langle$, Cl^-, Br^- soft, weak elie	Weak preferred e.g. HOH, ROH strong C^+ elie
Solvent	Aprotic preferred usually e.g. propanone, DMSO, DMF avoid H bonding of nuc^-	Protic preferred e.g. HOH, MeOH, EtOH H bond rls TS
Stereochemistry	Inversion of configuration stereoselective	Inversion & retention C^+ not stereoselective
C^+ rearrangement	Never no C^+	Sometimes for suitable C^+

rls = rate-limiting step; nuc = nucleophile; elie = electrophile

Puzzle 6.20 ───

To facilitate an S_N2 reaction at the expense of an S_N1 reaction, how should one adjust the following features?
(a) nucleophile concentration   (b) nucleophilicity   (c) solvent

Puzzle 6.21 ───

To facilitate an S_N1 reaction at the expense of an S_N2 reaction, how should one adjust the following features?
(a) nucleophile concentration   (b) nucleophilicity   (c) solvent

───

6.8 Synthetic Considerations

One important, challenging kind of problem in organic chemistry is determining reactants needed to make a desired organic compound. Solving these synthetic puzzles entails writing one or more reactions without writing the mechanistic steps.

A great variety of organic compounds can be synthesized by nucleophilic substitutions of alkyl halides. Our two kinds of nucleophilic substitutions, however, are not equally useful. With preferred methyl or primary halides, S_N2 reactions are generally better for synthesis because they tend to have fewer competing reactions. Even with preferred tertiary halides, S_N1 reactions are inevitably plagued by competing reactions. We will discuss this competition in the form of elimination reactions in Chapter 7.

An S_N2 reaction always forms a bond between the α carbon of the electrophile and the nucleophilic atom. The nucleophilic atom might be oxygen, nitrogen, carbon, phosphorous, sulfur or halogen. Table 6.6 shows some of the types of nucleophiles and products found in S_N2 reactions.

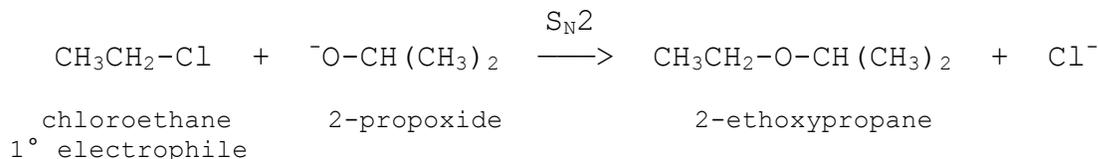Table 6.6 Types of Nucleophiles and Products in S$_N$2 Reactions

nuc¯ + R-X ⟶ nuc-R + X¯

Nucleophile	**S$_N$2 Product**	**Product name**
HÖ:¯	HO-R	Alcohol
R'-Ö:¯	R'-O-R	Ether
.. —N— │ ..	|+ —N-R │	Ammonium ion
.. —P— │ ..	|+ —P-R │	Phosphonium ion
HṢ:¯	HS-R	Thiol
R'-Ṣ:¯	R'-S-R	Thioether
:Ẋ:¯	X-R	Alkyl halide
N≡C:¯	N≡C-R	Nitrile
—C≡C:¯	—C≡C-R	Alkyne
R'-MgX (R':¯)	(poor reaction)	
R'-Li (R':¯)	(poor reaction)	

Let us solve a synthetic problem by setting up an S$_N$2 reaction with a strong S$_N$2 nucleophile and preferably a methyl or primary halide electrophile. Using a nucleophilic substitution, how could we synthesize the following compound?
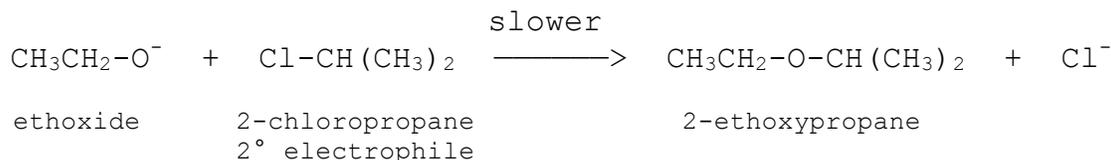
$$CH_3-CH_2-O-CH(CH_3)_2$$
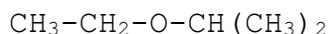
synthetic target, 2-ethoxypropane

First, we should locate the bond to be formed in the product. A good choice here is one of the two oxygen-carbon bonds because nucleophilic oxygens react well with electrophilic carbons. Because a primary halide surpasses a secondary halide as an S$_N$2 electrophile, we choose to make the bond between the oxygen and the *primary* carbon. Accordingly, the electrophile is any CH_3CH_2X, for example, CH_3CH_2Cl. The nucleophile must be strong and the nucleophilic atom must be oxygen. A good choice is ¯$OCH(CH_3)_2$, a strong, not too bulky base and so a strong nucleophile. Thus, a good method for synthesizing the desired product follows:

$$S_N2$$
$$CH_3CH_2\text{-}Cl \quad + \quad {}^-O\text{-}CH(CH_3)_2 \quad \xrightarrow{} \quad CH_3CH_2\text{-}O\text{-}CH(CH_3)_2 \quad + \quad Cl^-$$

  chloroethane   2-propoxide   2-ethoxypropane
1° electrophile

Consider a less effective synthesis of this ether:

$$\text{slower}$$
$$CH_3CH_2\text{-}O^- \quad + \quad Cl\text{-}CH(CH_3)_2 \quad \xrightarrow{} \quad CH_3CH_2\text{-}O\text{-}CH(CH_3)_2 \quad + \quad Cl^-$$

  ethoxide   2-chloropropane   2-ethoxypropane
                  2° electrophile

The more sterically hindered secondary electrophile slows this S_N2 reaction and allows more competition from elimination reactions (Chapter 7). Once again, a good sense of nucleophiles and electrophiles underlies understanding organic reactions.
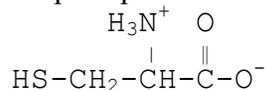
Puzzle 6.22 ──

Show feasible reactants that could readily yield the following products by nucleophilic substitutions:
(a) $N\equiv CCH_3$ (b) $(CH_3)_3CSCH_3$ (c) $CH_3CHOHCH_3$ (d) $CH_3CH_2NHCH_3$

Puzzle 6.23 ──

Cysteine is one the amino acids that compose proteins. In water at pH 7, it has this structure:
$$\overset{\displaystyle H_3N^+ \quad\;\; O}{\underset{\displaystyle HS\text{-}CH_2\text{-}CH\text{-}C\text{-}O^-}{\Big|\qquad\; \|}}$$
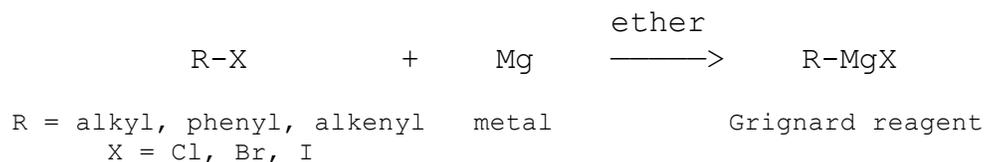Assume that you want to efficiently ethylate its sulfur.
(a) At about which $[H^+]$ would cysteine be in a form that allows ready ethylation of its sulfur. Use Table 4.1 (Section 4.2).
(b) Specify a reagent that would ethylate the cysteine's sulfur.
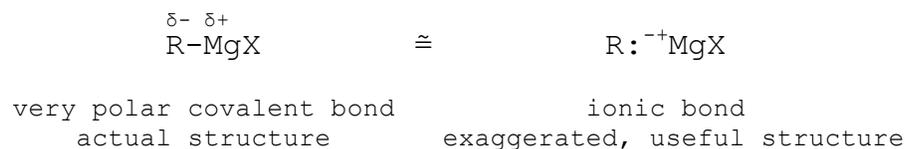
6.9 Grignard Reagents

Not all substitution reactions of alkyl halides are S_N1 or S_N2. A different kind of substitution reaction generates an interesting and important compound called a **Grignard reagent** (F. A. Victor Grignard, France, 1871-1935).

$$\text{ether}$$
$$R\text{-}X \qquad + \qquad Mg \qquad \xrightarrow{} \qquad R\text{-}MgX$$

  R = alkyl, phenyl, alkenyl   metal   Grignard reagent
      X = Cl, Br, I

Because carbon is bonded directly to magnesium, a Grignard reagent is also called an

organomagnesium reagent. It is made with magnesium metal, not a magnesium salt. This reaction works with any class of alkyl halide: methyl, primary, secondary, or tertiary. In addition, phenyl halides (Ph-X, Section 1.3B) and alkenyl halides (i.e., vinyl halides, –C=C-X) can generate Grignard reagents. The mechanism of this reaction is not well established but involves radicals with unpaired electrons. The ether solvent, usually diethyl ether (ethoxyethane) or tetrahydrofuran (oxolane), assists the reaction by solvating the Grignard reagent.

The unusual charge on the carbon group makes Grignard reagents so important:

$$\overset{\delta- \ \ \delta+}{\text{R-MgX}} \qquad \cong \qquad \text{R:}^{-+}\text{MgX}$$

```
        very polar covalent bond              ionic bond
            actual structure          exaggerated, useful structure
```
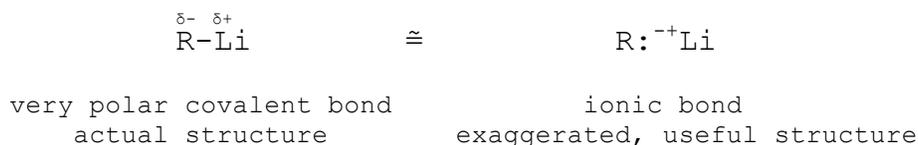
The 1.2 electronegativity of magnesium, a metal, is much less than the 2.5 electronegativity of carbon, a nonmetal (Table 1.7, Section 1.9A). The large difference greatly polarizes their covalent bond and gives the carbon a large partial negative charge, though not quite a formal anionic charge. Actually, the Grignard reagent reacts like a carbanion, so let us visualize and sometimes write the carbon with an exaggerated formal negative charge to express its reactivity.

Organolithium reagents resemble Grignard reagents in structure, preparation, and reactivity. They, too, have a metal attached to a carbon: RLi. They, too, are prepared by reacting a metal (not a salt) with an alkyl, phenyl, or alkenyl halide:
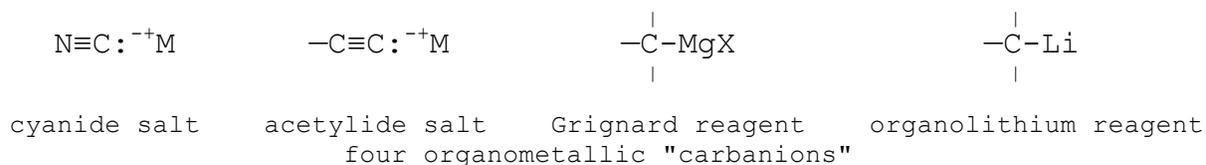
```
        R-X          +    2 Li   ⟶         R-Li          +     LiX

  R = alkyl, phenyl, alkenyl     metal       organolithium reagent
```
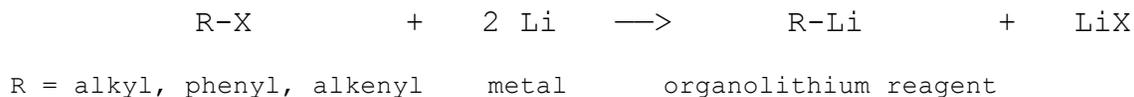
They, too, have a very polar covalent bond, which approximates an ionic bond and makes organolithium reagents react like carbanions:

$$\overset{\delta- \ \ \delta+}{\text{R-Li}} \qquad \cong \qquad \text{R:}^{-+}\text{Li}$$

```
        very polar covalent bond              ionic bond
            actual structure          exaggerated, useful structure
```
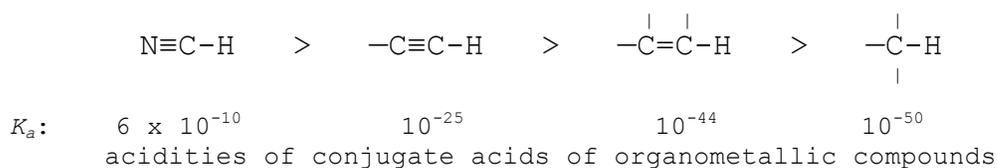
Indeed, the similarities between analogous organolithium and Grignard reagents are so strong that they are interchangeable in many reactions.

These are our first two types of **organometallic reagents,** which have a less electronegative metal directly attached to a carbon with a more or less full negative charge. Two other organometallic compounds are cyanide ion and acetylide ion salts:
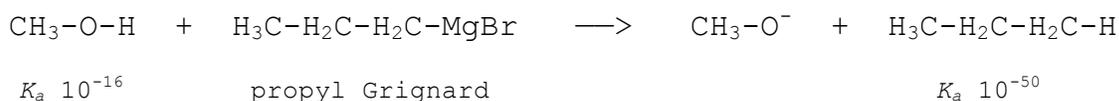
```
    N≡C:⁻⁺M          —C≡C:⁻⁺M              |                      |
                                         —C-MgX                 —C-Li
                                           |                      |

  cyanide salt    acetylide salt    Grignard reagent     organolithium reagent
                        four organometallic "carbanions"
```

M^+ symbolizes a metal ion, such as sodium or potassium ion. All four organometallic compounds are strong bases because carbon is neither electronegative nor soft enough to greatly stabilize its base electron pair (Sections 4.9A-B). Their weak conjugate acids with small K_a values confirm
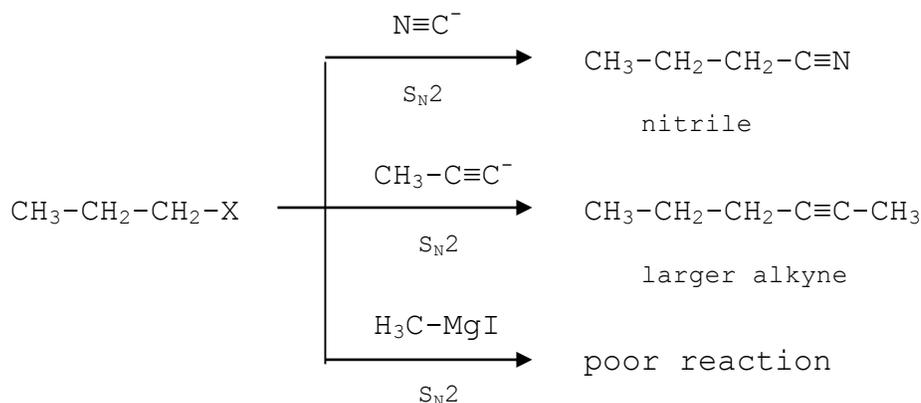
their strong basicities:

$$N{\equiv}C-H \quad > \quad -C{\equiv}C-H \quad > \quad -\overset{|}{C}{=}\overset{|}{C}-H \quad > \quad -\overset{|}{\underset{|}{C}}-H$$

K_a: 6 x 10^{-10} 10^{-25} 10^{-44} 10^{-50}
       acidities of conjugate acids of organometallic compounds

A Grignard (or organolithium) reagent is especially basic because of its sp^3 or sp^2, not sp, base atom (Section 4.9F).

   Their strong basicities make organometallic reagents very sensitive to acids, even when the carbanions are needed as non-base nucleophiles. Even the weakly acidic alcohols and water react very quickly with Grignard reagents. For example:

CH$_3$-O-H + H$_3$C-H$_2$C-H$_2$C-MgBr   ——>   CH$_3$-O$^-$ + H$_3$C-H$_2$C-H$_2$C-H

 K_a 10^{-16} propyl Grignard K_a 10^{-50}

So, it is important to avoid such protic functional groups in solvents and reagents when making Grignard reagents or when using them as non-base nucleophiles, their usual role.

   Yet, as strong bases, these organometallic reagents are also strong nucleophiles. Table 6.6 (Section 6.8) indicates that cyanide and acetylide ions react with suitable alkyl halides in S$_N$2 reactions. This table, however, also shows that a Grignard or organolithium reagent does not ordinarily react with these electrophiles in good yield. Other reactions, often involving radicals, give a mixture of products.


```
                          N≡C⁻
                    ───────────────>  CH₃-CH₂-CH₂-C≡N
                         S_N2
                                          nitrile

                          CH₃-C≡C⁻
CH₃-CH₂-CH₂-X      ───────────────>  CH₃-CH₂-CH₂-C≡C-CH₃
                         S_N2
                                       larger alkyne

                          H₃C-MgI
                    ───────────────>  poor reaction
                         S_N2
```

We will find a carbon electrophile appropriate for a Grignard reagent in Section 10.8B.

Puzzle 6.24 ───

Outline a synthesis of benzene from chlorobenzene.

Chapter Summary

1. The boiling points of simple alkyl halides increase with the size of the molecule because of increasing dispersion forces. Simple alkyl halides do not dissolve well in water.
2. An S_N2 reaction, a bimolecular nucleophilic substitution, is first order in both nucleophile and electrophile with a one-step mechanism.
3. An S_N2 reaction is stereoselective with inversion of configuration at the α carbon.
4. Alkyl substitution at the α carbon of the electrophile hinders an S_N2 reaction. So a methyl halide reacts fastest, whereas a tertiary halide is too bulky to react in an S_N2 reaction.
5. Because of its soft, weak electrophile, an S_N2 reaction with an alkyl halide requires a nucleophile that is a strong or a soft base. A nucleophile with very large overall bulk hinders an S_N2 reaction.
6. An S_N1 reaction, a unimolecular nucleophilic substitution, is first order in the electrophile and zero order in the nucleophile.
7. Both S_N2 and S_N1 reactions require an electrophile with a leaving group that is a stable, weak base, such as any of the halide ions.
8. In the first, rate-limiting step of the multistep mechanism, the S_N1 electrophile dissociates into a carbocation, the key factor in an S_N1 reaction.
9. Alkyl substitution at the α carbon of the electrophile promotes an S_N1 reaction by stabilizing the carbocation intermediate with hyperconjugation. Tertiary halides react fastest, whereas methyl and primary halides normally do not react by an S_N1 mechanism.
10. Because of its very reactive carbocation intermediate, an S_N1 reaction does not need a strong nucleophile but actually prefers a weak nucleophile that is weakly basic to minimize competing reactions.
11. Because of its symmetric, planar carbocation intermediate, a pure S_N1 reaction is not stereoselective.
12. Some S_N1 reactions undergo carbocation rearrangements to yield constitutional isomers.
13. An S_N1 reaction prefers a protic solvent to hydrogen bond with the anion generated in the rate-limiting step. An S_N2 reaction with an anionic nucleophile prefers an aprotic solvent to avoid hydrogen bonding with the nucleophile.
14. Having less competition, S_N2 reactions, especially those with methyl or primary halides, are generally used instead of S_N1 reactions to synthesize a wide variety of products.
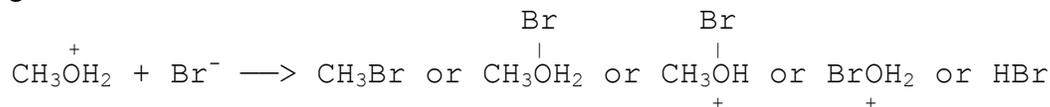
Additional Puzzles

6.25 In each of the following pairs, decide which compound has the higher boiling point. Explain each answer.
(a) $BrCH_2CH_3$, $BrCH_3$ (b) $CH_3CH_2CH_3$, $CH_3CHClCH_3$
(c) $BrCH_2CH_2CH_2CH_3$, $ICH_2CH_2CH_2CH_3$ (d) CH_3CHICH_3, $ClCH_2CH_3$

6.26 (a) How would doubling the volume of solution, by increasing the amount of solvent without increasing the amounts of nucleophile and electrophile, affect the rate of an S_N2 reaction and the rate of an S_N1 reaction?
(b) How could you adjust the amount of solvent to favor an S_N1 reaction over an S_N2 reaction?

6.27 Consider a nucleophilic substitution reaction of (R)-2-chloropentane with iodide ion.
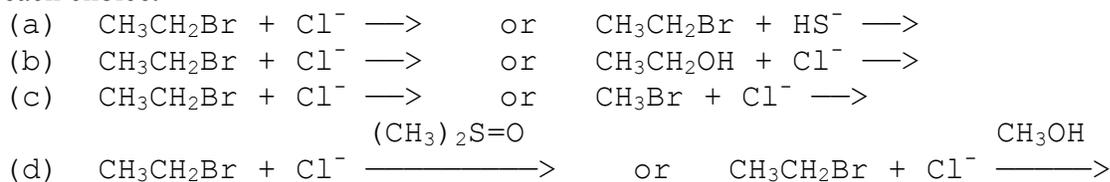(a) Suggest a solvent that would favor an S_N2 over an S_N1 reaction.
(b) Suggest a solvent that would favor an S_N1 over an S_N2 reaction.
(c) Show the mechanism for the S_N2 reaction with electrophile and organic product(s) in three dimensions.
(d) Show the mechanism for the S_N1 reaction with electrophile and organic product(s) in three dimensions.

6.28 Consider bromide ion bonding to an oxonium ion at the α carbon, the cationic oxygen, or the hydrogen in five different reactions:

```
                              Br          Br
         +                    |           |
   CH₃OH₂ + Br⁻ ——> CH₃Br or CH₃OH₂ or CH₃OH or BrOH₂ or HBr
                                                +        +
```

(a) Which of the products seem feasible? Explain in terms of leaving groups or the octet rule.
(b) Does the oxygen with its formal positive charge attract the nucleophile directly to it?

6.29 In each pair of nucleophilic substitution reactions, decide which will react faster. Explain each choice.

```
(a)   CH₃CH₂Br + Cl⁻ —>     or    CH₃CH₂Br + HS⁻ —>
(b)   CH₃CH₂Br + Cl⁻ —>     or    CH₃CH₂OH + Cl⁻ —>
(c)   CH₃CH₂Br + Cl⁻ —>     or    CH₃Br + Cl⁻ —>
                    (CH₃)₂S=O                              CH₃OH
(d)   CH₃CH₂Br + Cl⁻ ————————>     or    CH₃CH₂Br + Cl⁻ ————>
```

6.30 Consider all $C_7H_{13}Br$ constitutional isomers with a cyclohexane ring. Decide which should be most reactive in:
(a) a nucleophilic substitution reaction with hydroxide ion in propanone solvent.
(b) a nucleophilic substitution reaction with methanol solvent.

6.31 The rate of the nucleophilic substitution of 2-chloro-2-methylpropane in aqueous solution is largely unaffected by the presence or absence of a small amount of sodium hydrosulfide, NaSH. Yet the presence of sodium hydrosulfide leads to an additional organic product.
(a) Use this information alone to determine whether an S_N2 or S_N1 reaction is occurring?
(b) Indicate the organic products when the hydrosulfide is present.

6.32 Draw the organic products from the nucleophilic substitution reactions of chloroethane with the following reagents. Assume a suitable, unreactive solvent. If no such reaction occurs, say so.
(a) NaBr (b) LiOH (c) H₂O (d) H⁺ (e) H₂ (f) H₂NCH₃ (g) CH₃ONa (h) CH₃OH
(i) CH₃C≡CNa (j) LiCN (k) NaSH (l) NaSCH₃ (m) (C₆H₅)₃P

6.33 Draw the organic products from the nucleophilic substitution reactions of 2-chloro-2-methylpropane with the following reagents. Assume a suitable, unreactive solvent. If no such reaction occurs, say so.
(a) NaBr (b) LiOH (c) H₂O (d) H⁺ (e) H₂ (f) H₂NCH₃ (g) CH₃ONa (h) CH₃OH
(i) CH₃C≡CNa (j) LiCN (k) NaSH (l) NaSCH₃ (m) (C₆H₅)₃P

6.34 The cubic molecule below is whimsically called iodocubane.
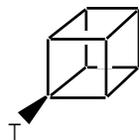
(a) Would it react readily in an S_N2 reaction? Explain.
(b) Why would it not react readily in an S_N1 reaction? Explain.

6.35 Benzyl bromide, C_6H_5-CH_2-Br, can react with water in an S_N1 reaction.
(a) Draw the mechanism and organic product.
(b) Why is the apparently primary carbocation intermediate feasible?

6.36 (a) Draw the mechanism for the reaction:
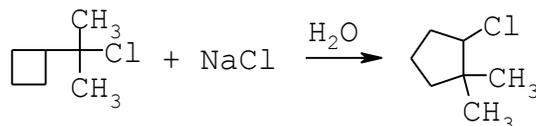
(b) What is the unusual kind of rearrangement during this reaction, and why does it occur?

6.37 In each pair of electrophiles, decide which compound would more quickly undergo an S_N2 reaction with an anion nucleophile. Then decide which compound would more quickly undergo an S_N1 reaction. Explain each choice.
(a) $(CH_3)_2CHCl$ or $(CH_3)_3CCl$ (b) $(CH_3)_2CHCl$ or $(CH_3)_2CHI$
(c) $(CH_3)_2CHCl$ in dimethylsulfoxide (DMSO) or in ethanol

6.38 (a) How can chloroethane be converted into a stable organic compound that is very soluble in water.
(b) Explain why the product is soluble in water.
(c) Which organic compound, the reactant or product, has the higher boiling point? Explain.

6.39 Find a *single* alkyl halide that can be converted into all of the following products:
(a) $BrCH_2CH_2CH_3$ (b) $CH_3CH_2CH_2SH$ (c) $CH_3CH_2CH_2OCH_3$ (d) $HC{\equiv}CCH_2CH_2CH_3$
(e) $CH_3CH_2CH_2C{\equiv}N$ (f) $CH_3CH_2CH_2OH$ (g) $CH_3CH_2NHCH_2CH_2CH_3$
Indicate the reagent(s) needed for each conversion.

6.40   One molecule of 4-bromobutylamine, $H_2NCH_2CH_2CH_2CH_2Br$, reacts with itself in an intramolecular nucleophilic substitution reaction to form a cyclic compound.
(a) Draw the cyclic product and the mechanism.   (b) Write the rate equation.
A competing reaction is intermolecular nucleophilic substitution between two molecules of 4-bromobutylamine.
(c) Draw the organic product.   (d) Write the rate equation.
(e) Suggest a way to favor the cyclization over the competing reaction.

6.41 Consider the nucleophilic substitution reaction:

ethyl tosylate
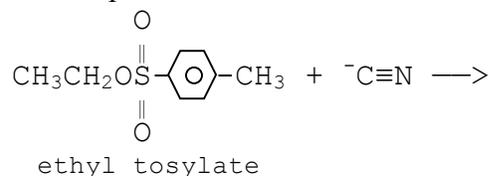
(a) With the help of Table 4.1 (Section 4.2), evaluate tosylate ion ($^-OSO_2C_6H_4CH_3$) as a leaving group.
(b) Draw the organic products from this substitution reaction, if any.

6.42 From what acyclic organic compound could you synthesize the following compound?

6.43   When (R)-2-bromobutane and lithium bromide are dissolved in acetone, the solution eventually becomes optically inactive (Section 3.1C). Explain with a mechanism.

6.44 Geranyl pyrophosphate is a metabolite during the biosynthesis of terpenes, essential oils that give plants distinctive smells and tastes. Geranyl pyrophosphate can undergo S_N1 hydrolysis to become the terpene nerol, which smells like roses:
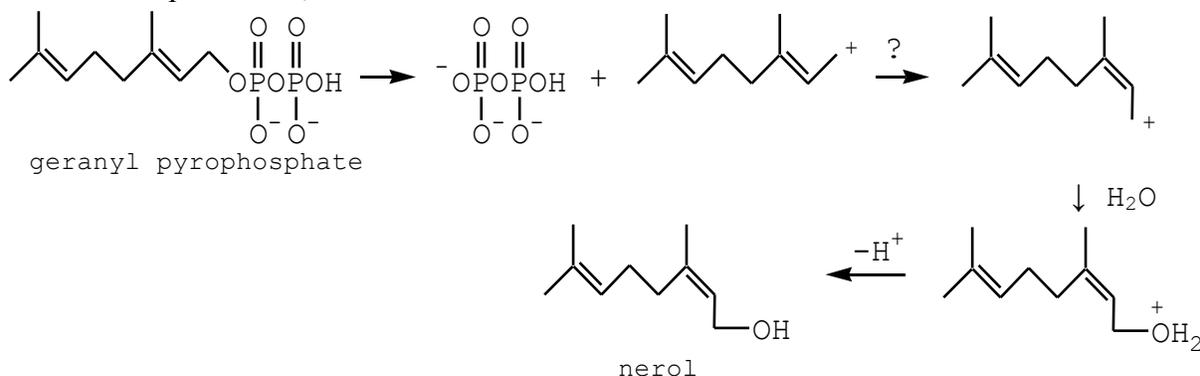
(a)   Normal primary carbocations are very difficult to form. What structural feature greatly stabilizes the apparent primary carbocations above?
(b) Explain how the first carbocation isomerizes to the second carbocation.